Postpartum haemorrhage: prevention

Search date March 2010

David Chelmow

ABSTRACT

INTRODUCTION: Loss of more than 500 mL of blood following childbirth is usually caused by failure of the uterus to contract fully after delivery of the placenta, and occurs in over 10% of deliveries, with a 1% mortality rate worldwide. Other causes of postpartum haemorrhage include retained placental tissue, lacerations to the genital tract, and coagulation disorders. Uterine atony is more likely in women who have had a general anaesthetic or oxytocin, an over-distended uterus, a prolonged or precipitous labour, or who are of high parity. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of non-drug interventions and of drug interventions to prevent primary postpartum haemorrhage? We searched: Medline, Embase, The Cochrane Library, and other important databases up to March 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 40 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: active management of the third stage of labour, carboprost injection, controlled cord traction, ergot compounds (ergometrine/methylergotamine), immediate breastfeeding, misoprostol (oral, rectal, sublingual, or vaginal), oxytocin, oxytocin plus ergometrine combinations, prostaglandin E2 compounds, and uterine massage.

QUESTIONS

INTERVENTIONS

Key points

- Loss of more than 500 mL of blood is usually caused by failure of the uterus to contract fully after delivery of the placenta, and occurs in over 10% of deliveries, with a 1% mortality worldwide.

  Other causes of postpartum haemorrhage include retained placental tissue, lacerations to the genital tract, and coagulation disorders.

  Uterine atony is more likely in women who have had a general anaesthetic or oxytocin, an over-distended uterus, a prolonged or precipitous labour, or who are of high parity.

- Active management of the third stage of labour, with controlled cord traction, early cord clamping plus drainage, and prophylactic oxytocic agents, reduces the risk of postpartum haemorrhage and its complications.

  Active management increases nausea, vomiting, and headache, but generally improves maternal satisfaction.

  Controlled cord traction may reduce the risk of retained placenta and need for medical treatment, and can be used in any resource setting.

  Uterine massage is often used to prevent postpartum haemorrhage, and is supported by a single RCT. It can be used in any resource setting.

- Oxytocin has been shown to effectively reduce the risk of postpartum haemorrhage compared with placebo.

A combination of oxytocin plus ergometrine may be slightly more effective than oxytocin alone, although there are more adverse effects.

- Ergot alkaloids seem as effective as oxytocin, but are also associated with adverse effects including nausea, placenta retention, and hypertension.
- Prostaglandin treatments vary in their efficacy, but are all associated with adverse effects.

  Carboprost and prostaglandin E2 compounds may be as effective as oxytocin and ergot compounds, but have gastrointestinal adverse effects, such as diarrhoea.

  Misoprostol seems ineffective compared with placebo when administered orally, rectally, or vaginally, and is associated with adverse effects including shivering and fever. However, rectal misoprostol may be as effective as oxytocin.

  Sublingually administered misoprostol may be more effective than placebo in preventing postpartum haemorrhage (evidenced by a single RCT). Sublingual misoprostol has similar effects to injected agents, but is associated with more adverse effects.

  When available, oxytocin, ergometrine, or combinations are preferred to misoprostol, as misoprostol seems less effective and is associated with more adverse effects. Sublingual administration is the preferred route for misoprostol.

DEFINITION

Postpartum haemorrhage is characterised by an estimated blood loss greater than 500 mL. The leading cause of postpartum haemorrhage is uterine atony — the failure of the uterus to contract fully after delivery of the placenta. Postpartum haemorrhage is divided into immediate (primary) and delayed (secondary). Primary postpartum haemorrhage occurs within the first 24 hours after delivery, whereas secondary postpartum haemorrhage occurs between 24 hours and 6 weeks after delivery. This review addresses the effects of strategies for prevention of postpartum haemorrhage after vaginal delivery in low- and high-risk women, specifically looking at strategies to prevent uterine atony. Future updates will examine strategies to prevent postpartum haemorrhage due to other causes, as well as treatment strategies.

INCIDENCE/ PREVALENCE

The WHO reports that obstetric haemorrhage causes 127,000 deaths annually worldwide and is the world's leading cause of maternal mortality. Nearly all of these deaths are due to postpartum haemorrhages, which occur nearly 14 million times each year. [1] In Africa, haemorrhage is estimated to be responsible for 30% of all maternal deaths. [2] The imbalance between resource-rich and resource-poor areas probably stems from a combination of: increased prevalence of risk factors such as grand multiparity, lack of safe blood banking, no routine use of prophylaxis against haemorrhage, and lack of measures for drug and surgical management of atony.

AETIOLOGY/ RISK FACTORS

In addition to uterine atony, immediate postpartum haemorrhage is frequently caused by: retained placental tissue; trauma such as laceration of the perineum, vagina, or cervix; rupture of the uterus; or coagulopathy. Risk factors for uterine atony include: use of general anaesthetics; an over-distended uterus, particularly from multiple gestations, a large fetus, or polyhydramnios; prolonged labour; precipitous labour; use of oxytocin for labour induction or augmentation; high parity; chorioamnionitis; or history of atony in a previous pregnancy.

PROGNOSIS

Most postpartum haemorrhage, particularly in Europe and the US, is well tolerated by women. However, in low-resource settings, where women may already be significantly anaemic during pregnancy, blood loss of 500 mL is significant. Although pregnancy-related death is rare in the US, postpartum haemorrhage accounts for 17% of deaths. [3] Maternal death is 50 to 100 times more frequent in resource-poor countries, and postpartum haemorrhage is responsible for a similar proportion of deaths as in the US. Other significant morbidities associated with postpartum haemorrhage include renal failure, respiratory failure, multiple organ failure, need for transfusion, need for surgery including dilatation and curettage, and, rarely, hysterectomy. Some women with large blood loss will later develop Sheehan's syndrome.

AIMS OF INTERVENTION

To prevent death; to reduce volume of blood loss, need for manual removal of placenta, need for transfusion, and need for medical or surgical treatment of postpartum haemorrhage.

OUTCOMES

Maternal **mortality**; **postpartum haemorrhage** (includes volume of blood loss, blood loss estimated by drop in haemoglobin or haematocrit, and need for transfusion); **maternal morbidity** (includes renal failure, multiple organ failure, and respiratory failure); **need for additional medical treatment** (includes need for admission to an intensive care unit, drug treatment); **need for additional surgical treatment** (includes hysterectomy and manual removal of the placenta); **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal March 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to March 2010, Embase 1980 to March 2010, and The Cochrane Database of Systematic Reviews 2010, Issue 2 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using pre-determined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, containing more than 40 women of whom more than 80% were followed up. The minimum length of follow-up required to include studies was 24 hours for most outcomes. We included open studies. We also included systematic reviews of RCTs and RCTs where harms of an included intervention were studied, applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 107). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of non-drug interventions to prevent primary postpartum haemorrhage?**

OPTION ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Active management of the third stage of labour, with controlled cord traction, early cord clamping plus drainage, and prophylactic oxytocic agents, reduces the risk of postpartum haemorrhage and its complications.
- Active management increases nausea, vomiting, and headache, but generally improves maternal satisfaction.

Benefits and harms

Active management versus expectant management or oxytocin:

We found one systematic review (search date 2000), which identified 5 RCTs including 6477 women in maternity units in the UK (4 RCTs) and in the United Arab Emirates (1 RCT). Three were in low-risk populations, and risk status was not specified in the other two. [4]

Postpartum haemorrhage

Compared with expectant management or with expectant management plus routine oxytocin Active management of the third stage of labour, consisting of controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent, is more effective at reducing postpartum haemorrhage (blood loss of at least 500 mL). Active management is also more effective at reducing need for blood transfusion and postpartum haemoglobin less than 9 g/dL (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[4] Systematic review	6284 women 4 RCTs in this analysis	**Severe postpartum haemorrhage (defined as clinically estimated blood loss of at least 1000 mL)** 27/3126 (1%) with active management 83/3158 (3%) with expectant management alone or oxytocin alone	RR 0.33 95% CI 0.21 to 0.51	●●○	active management

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details			
[4] Systematic review	6284 women 4 RCTs in this analysis	**Postpartum haemorrhage** 163/3126 (5%) with active management 428/3158 (14%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 0.38 95% CI 0.32 to 0.46	●●○	active management
[4] Systematic review	3124 women 2 RCTs in this analysis	**Secondary postpartum haemorrhage** 20/1551 (1%) with active management 23/1573 (2%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 0.88 95% CI 0.49 to 1.60	⟷	Not significant
Blood transfusion					
[4] Systematic review	6477 women 5 RCTs in this analysis	**Need for transfusion** 25/3229 (1%) with active management 75/3248 (2%) with expectant management alone or combined with oxytocin The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 0.34 95% CI 0.22 to 0.53	●●○	active management
Postpartum haemoglobin/haematocrit level					
[4] Systematic review	4255 women 4 RCTs in this analysis	**Postpartum haemoglobin level <9 g/dL** 52/2108 (3%) with active management 132/2147 (6%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 0.40 95% CI 0.29 to 0.55	●●○	active management

Need for additional medical treatment

Compared with expectant management or expectant management plus routine oxytocin Active management of the third stage of labour, consisting of controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent, is more effective at reducing the need for additional medical treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[4] Systematic review	6477 women 5 RCTs in this analysis	**Need for additional medication** 112/3229 (4%) with active management 555/3248 (17%) with expectant management alone or combined with oxytocin The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR. 0.20 95% CI 0.17 to 0.25	●●○	active management

Need for additional surgical treatment

Compared with expectant management or expectant management plus routine oxytocin Active management of the third stage of labour, consisting of controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent, seems no more effective at reducing the need for manual or surgical removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Removal of retained placental tissue					
[4] Systematic review	4636 women 3 RCTs in this analysis	**Need for surgical removal of retained placental tissue** 22/2299 (1%) with active management 30/2337 (1%) with expectant management alone or combined with oxytocin The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR. 0.74 95% CI 0.43 to 1.28	⟷	Not significant
[4] Systematic review	6477 women 5 RCTs in this analysis	**Need for manual removal of the placenta** 54/3229 (2%) with active management 45/3248 (1%) with expectant management alone or combined with oxytocin The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 1.21 95% CI 0.82 to 1.78 One RCT in the meta-analysis found difference between groups to be significant; see further information on studies for full details	⟷	Not significant

Mortality

No data from the following reference on this outcome. [4]

Maternal morbidity

No data from the following reference on this outcome. [4]

Adverse effects

Compared with expectant management alone or in combination with oxytocin Active management is associated with a higher rate of adverse effects such as nausea and vomiting (high-quality evidence). However, active management reduces the length of the third stage of labour, and women are less likely to be dissatisfied when their third stage of labour is actively managed.

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[4] Systematic review	3407 women 3 RCTs in this analysis	**Nausea** 247/1680 (15%) with active management 139/1727 (8%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 1.83 95% CI 1.51 to 2.23	●○○	expectant management
[4] Systematic review	3407 women 3 RCTs in this analysis	**Vomiting** 159/1680 (10%) with active management 74/1727 (4%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 2.19 95% CI 1.68 to 2.86	●●○	expectant management
Headache					
[4] Systematic review	3407 women 3 RCTs in this analysis	**Headache** 24/1678 (1%) with active management 13/1727 (0.8%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 1.97 95% CI 1.01 to 3.82	●○○	expectant management
Other adverse effects					
[4] Systematic review	1429 women Data from 1 RCT	**Bleeding needing readmission or antibiotics** 5/705 (0.7%) with active management 0/724 (0%) with expectant management alone or oxytocin alone The RCTs used a range of oxytocic agents as part of active management; see further information on studies for full details	RR 11.30 95% CI 0.63 to 203.92	⟷	Not significant
[4] Systematic review	1557 women Data from 1 RCT	**Maternal fatigue , 6 weeks** 105/745 (14%) with active management 113/752 (15%) with expectant management alone or combined with oxytocin The RCTs used a range of oxytocic agents as part of active man-	RR 0.95 95% CI 0.74 to 1.22	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		agement; see further information on studies for full details			

Further information on studies

[4] **Interventions used** All women in the active-management group received controlled cord traction, early cord clamping plus drainage, and a prophylactic oxytocic agent. The RCTs used a range of oxytocic agents as part of active management, with oxytocin alone given in one RCT, ergometrine in one RCT, and a fixed combination of oxytocin plus ergometrine in the other three. Four RCTs compared active management versus expectant management, whereas one RCT used iv oxytocin alone after placental delivery as control intervention. All but one RCT limited entry to women with singleton vertex deliveries. **Need for manual placenta removal** Four RCTs included in the meta-analysis found no significant difference between interventions, but one RCT (using iv ergotamine as the oxytocic agent) found the need for manual placenta removal to be much higher with active management, thus skewing the pooled estimate compared with the control intervention. **Patient dissatisfaction** Despite the increased risk of adverse effects, a significantly smaller proportion of women reported dissatisfaction with their third-stage management when it was actively managed (1 RCT, 1466 women; 27/748 [4%] with active management *v* 46/718 [6%] with expectant management; RR 0.56, 95% CI 0.35 to 0.90).

Comment: The review assessed in this option was withdrawn from The Cochrane Library in Issue 3, 2009 as it is out of date. A protocol for the update of this review was available in Issue 2, 2010 of The Cochrane Library but the fully updated review has not yet been published.

OPTION CONTROLLED CORD TRACTION

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Controlled cord traction may reduce the risk of retained placenta and need for medical treatment, and can be used in any resource setting.

Benefits and harms

Controlled cord traction versus minimal intervention:

We found one systematic review (search date not reported) comparing controlled cord traction alone versus minimal intervention, which identified two quasi-randomised trials, neither of which met *Clinical Evidence* inclusion criteria. [5] We found two additional RCTs [6] [7] and one subsequent RCT. [8]

Postpartum haemorrhage

Compared with minimal intervention Controlled cord traction plus uterine massage, with or without oxytocin, may be more effective than minimal intervention at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL). We don't know whether controlled cord traction is more effective at reducing need for transfusion or rate of shock (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[7] RCT **5-armed trial**	300 women having vaginal deliveries in a hospital in China The remaining arms evaluated rectal carboprost, oxytocin alone, and oxytocin plus controlled cord	**Estimated blood loss** 147 mL with controlled cord traction plus uterine massage 244 mL with minimal intervention (normal saline)	P less than or equal to 0.01	○○○	controlled cord traction

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	traction plus uterine massage				
[7] RCT **5-armed trial**	300 women having vaginal deliveries in a hospital in China The remaining arms evaluated rectal carboprost, oxytocin alone, and oxytocin plus controlled cord traction plus uterine massage	**Proportion of women with blood loss >500 mL** 2% with controlled cord traction plus uterine massage 8% with minimal intervention (normal saline)	Significance not assessed		
[7] RCT **5-armed trial**	300 women having vaginal deliveries in a hospital in China The remaining arms evaluated rectal carboprost, controlled cord traction plus uterine massage, and normal saline	**Estimated blood loss** 120 mL with controlled cord traction plus oxytocin plus uterine massage 172 mL with minimal intervention (oxytocin only)	P less than or equal to 0.01	○○○	controlled cord traction plus oxytocin
[7] RCT **5-armed trial**	300 women having vaginal deliveries in a hospital in China The remaining arms evaluated rectal carboprost, controlled cord traction plus uterine massage, and normal saline	**Proportion of women with blood loss >500 mL** 0% with controlled cord traction plus oxytocin plus uterine massage 5% with minimal intervention (oxytocin only)	Significance not assessed		
[8] RCT	204 women having vaginal deliveries at two hospitals in Uruguay, all receiving oxytocin and uterine massage	**Proportion of women with blood loss >500 mL** 17/101 (17%) with controlled cord traction 22/98 (23%) with no cord contraction ("hands off" management protocol)	RR 0.74 95% CI 0.42 to 1.32	⟷	Not significant
[8] RCT	204 women having vaginal deliveries at two hospitals in Uruguay, all receiving oxytocin and uterine massage	**Proportion of women with blood loss >1000 mL** 1/101 (3%) with controlled cord traction 5/98 (5%) with no cord contraction ("hands off" management protocol)	RR 0.58 95% CI 0.14 to 2.37	⟷	Not significant
Blood transfusion					
[6] RCT	1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates	**Need for transfusion** 1/827 (0.1%) with controlled cord traction 4/821 (0.5%) with minimal intervention Both groups had early cord clamping and received oxytocin, although at different times; see further information on studies	OR 0.25 95% CI 0.01 to 2.33 Results should be interpreted with caution because of difference in time and mode of oxytocin administration	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[6] RCT	1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates	**Rates of shock** 2/827 (0.2%) with controlled cord traction 8/821 (1%) with minimal intervention Both groups had early cord clamping and received oxytocin, although at different times; see further information on studies	RR 0.25 95% CI 0.04 to 1.25 Results should be interpreted with caution because of difference in time and mode of oxytocin administration	⟷	Not significant

Need for additional medical treatment

Compared with minimal intervention Controlled cord traction seems more effective than minimal intervention at reducing the need for further medical treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[6] RCT	1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates	**Need for further medical treatment** 19/827 (2%) with controlled cord traction 42/821 (5%) with minimal intervention Both groups had early cord clamping and received oxytocin, although at different times; see further information on studies	OR 0.44 95% CI 0.24 to 0.78 Results should be interpreted with caution because of difference in time and mode of oxytocin administration	●●○	controlled cord traction
[8] RCT	204 women having vaginal deliveries at 2 hospitals in Uruguay, all receiving oxytocin and uterine massage	**Use of additional oxytocic agent** 13/96 (13.5%) with controlled cord traction 13/94 (13.8%) with minimal intervention	RR 0.98 95% CI 0.48 to 2.00	○○○	

No data from the following reference on this outcome. [7]

Need for additional surgical treatment

Compared with minimal intervention Controlled cord traction seems more effective than minimal intervention at reducing the risk of placental tissue retention at 30 minutes, but not at 60 minutes (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retention of placental tissue					
[6] RCT	1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates	**Risk of retained placental tissue , 30 minutes** 12/827 (1%) with controlled cord traction 37/821 (5%) with minimal intervention Both groups had early cord clamping and received oxytocin, although at different times; see further information on studies	OR 0.31 95% CI 0.15 to 0.63 Results should be interpreted with caution because of difference in time and mode of oxytocin administration	●●○	controlled cord traction

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[6] RCT	1648 low-risk women in the third stage of labour at a maternity unit in Abu Dhabi, United Arab Emirates	**Risk of retained placental tissue , 60 minutes** 3/827 (0.4%) with controlled cord traction 9/821 (1.1%) with minimal intervention Both groups had early cord clamping and received oxytocin, although at different times; see further information on studies	OR 0.33 95% CI 0.07 to 1.32 Results should be interpreted with caution because of difference in time and mode of oxytocin administration	⟷	Not significant
[8] RCT	204 women having vaginal deliveries at 2 hospitals in Uruguay, all receiving oxytocin and uterine massage	**Need for further intervention** with controlled cord traction with minimal intervention Absolute results not reported	Incidences of membrane retention, manual extraction of the placenta, or examination under general anaesthetic occurred in 3 women and were similar between the groups No uterine inversions were observed		

No data from the following reference on this outcome. [7]

Mortality

No data from the following reference on this outcome. [6] [7] [8]

Maternal morbidity

No data from the following reference on this outcome. [6] [7] [8]

Adverse effects

No data from the following reference on this outcome. [6] [7] [8]

Controlled cord traction plus immediate cord drainage versus expectant management:

We found no systematic review but found one RCT. [9]

Postpartum haemorrhage

Compared with expectant management We don't know whether controlled cord traction plus immediate cord drainage is more effective than expectant management at reducing the drop in haemoglobin levels or the need for transfusion (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemoglobin level					
[9] RCT	477 low-risk women in France	**Median haemoglobin drop** 0.95 g/dL with controlled cord traction plus drainage 1.40 g/dL with expectant management Neither group received an oxytocic agent The exact timing of cord drainage in the active group was not specified	P = 0.0002	○○○	controlled cord traction plus drainage
[9] RCT	477 low-risk women in France	**Postpartum haemoglobin levels** 11.2 g/dL with controlled cord traction plus drainage 10.9 g/dL with expectant management Neither group received an oxytocic agent The exact timing of cord drainage in the active group was not specified	P = 0.09	⟷	Not significant
[9] RCT	477 low-risk women in France	**Proportion of women with postpartum haemoglobin levels <10 g/dL** 51/239 (21%) with controlled cord traction plus drainage 56/238 (24%) with expectant management Neither group received an oxytocic agent The exact timing of cord drainage in the active group was not specified	P = 0.07	⟷	Not significant
Blood transfusion					
[9] RCT	477 low-risk women in France	**Need for transfusion** 0/239 (0%) with controlled cord traction plus drainage 1/239 (1%) with expectant management Neither group received an oxytocic agent The exact timing of cord drainage in the active group was not specified	P = 0.50	⟷	Not significant

Need for additional surgical treatment

Compared with expectant management Controlled cord traction plus immediate cord drainage is no more effective than expectant management at reducing the need for manual removal of the placenta (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[9] RCT	477 low-risk women in France	**Need for manual removal of the placenta**	P = 0.13	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		18/239 (8%) with controlled cord traction plus drainage 20/238 (8%) with expectant management Neither group received an oxytocic agent The exact timing of cord drainage in the active group was not specified			

Mortality

No data from the following reference on this outcome. [9]

Maternal morbidity

No data from the following reference on this outcome. [9]

Need for additional medical treatment

No data from the following reference on this outcome. [9]

Adverse effects

No data from the following reference on this outcome. [9]

Further information on studies

[6] The cord-traction group received im oxytocin 10 IU at delivery of the anterior shoulder of the baby, whereas the control group had a continuous infusion after delivery of the placenta.

[8] The trial methods stated that blood would be collected from all women for 20 minutes post-delivery and drapes would not be removed until the bleeding had stopped. Lost blood was collected for 20 minutes from at least 95% of the women in both groups. The mean time of collection was 1.2 minutes longer in the comparison group, and this difference was significant (P = 0.02). The authors concluded that a longer collection period could have contributed to a greater recorded blood loss in the control group. The reasons for longer collection period in the control group are uncertain. The authors hypothesise that it could have been related to the intervention instructions for the control group, or to the clinical condition of the women. This may have biased results in favour of the intervention group, although if brisk bleeding had ceased prior to removing the drapes, 1 minute of additional drape time should not have significantly changed the amount of total blood collected.

Comment: **Clinical guide:**
Controlled cord traction can be used in any resource setting.

OPTION IMMEDIATE BREASTFEEDING

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- We found no clinically important results from RCTs about the effects of immediate breastfeeding on postpartum haemorrhage.

Benefits and harms

Immediate breastfeeding:

We found no systematic review or RCTs examining the effects of immediate breastfeeding on postpartum haemorrhage.

Further information on studies

Comment: **Clinical guide:**
Immediate breastfeeding is an attractive option in low-resource settings, and can reduce neonatal mortality. [10] However, there is insufficient evidence to judge whether it has an effect on reducing the risk of postpartum haemorrhage.

OPTION UTERINE MASSAGE

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Uterine massage is often used to prevent postpartum haemorrhage and is supported by a single RCT. It can be used in any resource setting.

Benefits and harms

Uterine massage plus active management versus active management:

We found one systematic review (search date 2004), [11] which identified one RCT. [12] The RCT compared uterine massage plus routine active management versus routine active management alone. [12]

Postpartum haemorrhage

Uterine massage with active management compared with active management alone Intermittent uterine massage every 10 minutes for an hour, plus active management, is no more effective than active management alone at reducing postpartum haemorrhage (blood loss of at least 500 mL) but is more effective at reducing blood loss volume at 30 and 60 minutes (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[12] RCT	200 women who delivered without obvious genital trauma In review [11]	**Postpartum haemorrhage (blood loss of at least 500 mL)** 4/98 (5%) with uterine massage (every 10 minutes for 60 minutes) plus routine active management (oxytocin 10 IU, iv or im) 8/102 (7%) with routine active management (oxytocin 10 IU, iv or im)	RR 0.52 95% CI 0.16 to 1.67	⟷	Not significant
Blood loss (volume)					
[12] RCT	200 women who delivered without obvious genital trauma	**Blood loss , 30 minutes** 168.8 mL with uterine massage (every 10 minutes for 60 minutes)	Mean difference –41.6 mL 95% CI –75.7 mL to –7.5 mL P = 0.017	○○○	uterine massage

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [11]	plus routine active management (oxytocin 10 IU, iv or im) 210.4 mL with routine active management (oxytocin 10 IU, iv or im)			
[12] RCT	200 women who delivered without obvious genital trauma In review [11]	**Blood loss , 60 minutes** 204.3 mL with uterine massage (every 10 minutes for 60 minutes) plus routine active management (oxytocin 10 IU, iv or im) 281.7 mL with routine active management (oxytocin 10 IU, iv or im)	Mean difference –77.4 mL 95% CI –119.2 mL to –35.5 mL P <0.001	○○○	uterine massage

Need for additional medical treatment

Uterine massage with active management compared with active management alone Intermittent uterine massage every 10 minutes for an hour, plus active management, is more effective than active management alone at reducing the need for an additional uterotonic agent (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[12] RCT	200 women who delivered without obvious genital trauma In review [11]	**Additional uterotonic** 5/98 (6%) with uterine massage (every 10 minutes for 60 minutes) plus routine active management (oxytocin 10 IU, iv or im) 26/102 (25%) with routine active management (oxytocin 10 IU, iv or im)	RR 0.20 95% CI 0.08 to 0.50	●●○	uterine massage

Mortality

No data from the following reference on this outcome. [12]

Maternal morbidity

No data from the following reference on this outcome. [12]

Need for additional surgical treatment

No data from the following reference on this outcome. [12]

Adverse effects

No data from the following reference on this outcome. [12]

Further information on studies

Comment: **Clinical guide:**
Uterine massage is frequently performed immediately after placental delivery. It is generally believed to help contract the uterus and to decrease blood loss, but it can be uncomfortable for the woman. Given the small likelihood of harm, it is reasonable to include this in standard management given the single supportive study.

QUESTION What are the effects of drug interventions to prevent primary postpartum haemorrhage?

OPTION OXYTOCIN

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Oxytocin has been shown to effectively reduce the risk of postpartum haemorrhage compared with placebo.
- A combination of oxytocin plus ergometrine may be slightly more effective than oxytocin alone, although there are more adverse effects.

Benefits and harms

Oxytocin versus placebo/no intervention:

We found one systematic review (search date 2004 [13]); see further information on studies for details of RCTs identified by the review.

Postpartum haemorrhage

Compared with placebo/no intervention Oxytocin (given at various stages of delivery) is more effective than placebo or no intervention at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) and at reducing rate of maternal postpartum anaemia or low levels of haemoglobin, but it seems no more effective at reducing the need for blood transfusion after expectant management (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[13] Systematic review	2243 women 4 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Severe postpartum haemorrhage (defined as clinically estimated blood loss of at least 1000 mL)** 48/1107 (4%) with oxytocin 83/1136 (7%) with placebo/no intervention	RR 0.61 95% CI 0.44 to 0.87	●○○	oxytocin
[13] Systematic review	1221 women 2 RCTs in this analysis	**Severe postpartum haemorrhage (defined as clinically estimated blood loss of at least 1000 mL)** 39/591 (7%) with oxytocin after expectant management of third stage of labour 59/630 (9%) with expectant management alone	RR 0.73 95% CI 0.49 to 1.07	⟷	Not significant
[13] Systematic review	3193 women 6 RCTs in this analysis	**Postpartum haemorrhage (defined as clinically estimated blood loss of at least 500 mL)** 188/1582 (12%) with oxytocin	RR 0.50 95% CI 0.43 to 0.59	●○○	oxytocin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	1 quasi-RCT included in meta-analysis	391/1611 (24%) with placebo/no intervention			
[13] Systematic review	1221 women 2 RCTs in this analysis	**Postpartum haemorrhage (defined as clinically estimated blood loss of at least 500 mL)** 129/591 (22%) with oxytocin after expectant management of third stage of labour 230/630 (37%) with expectant management alone	RR 0.61 95% CI 0.51 to 0.73	●○○	oxytocin after expectant management
Blood loss (volume)					
[13] Systematic review	1373 women 4 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Mean blood loss** with oxytocin with placebo/no intervention Absolute results not reported	Mean difference –102 mL 95% CI –135 mL to –59 mL	○○○	oxytocin
Blood transfusion					
[13] Systematic review	1221 women 2 RCTs in this analysis	**Need for blood transfusion** 9/591 (2%) with oxytocin 8/630 (1%) with placebo/no intervention	RR 1.30 95% CI 0.50 to 3.39	⟷	Not significant
Postpartum haemoglobin/haematocrit level					
[13] Systematic review	933 women Data from 1 RCT	**Maternal postpartum haemoglobin <9 g/dL** 20/485 (4%) with oxytocin 30/458 (7%) with placebo/no intervention	RR 0.63 95% CI 0.36 to 1.09	⟷	Not significant
[14] RCT	130 women in Tunisia expecting single, uncomplicated, full-term vaginal deliveries	**Postpartum anaemia (haemoglobin level <10 g/dL)** 17/65 (26%) with oxytocin (5 IU at time of delivery) 29/65 (45%) with no oxytocin All women received immediate cord clamping and controlled cord traction	RR 0.44 95% CI 0.21 to 0.92	●●○	oxytocin
[14] RCT	130 women in Tunisia expecting single, uncomplicated, full-term vaginal deliveries	**Mean haemoglobin drop** 0.51 g/dL with oxytocin (5 IU at time of delivery) 1.20 g/dL with no oxytocin All women received immediate cord clamping and controlled cord traction	Mean difference: –0.69 g/dL 95% CI –1.13 g/dL to –0.25 g/dL	○○○	oxytocin

Need for additional medical treatment

Compared with placebo/no intervention Oxytocin (given at various stages of delivery) seems more effective than placebo or no intervention at reducing the need for additional medical treatment of postpartum haemorrhage (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional medical treatment					
[13] Systematic review	2327 women 4 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Need for additional medical treatment** with oxytocin with placebo Absolute results not reported	RR 0.50 95% CI 0.39 to 0.64	●○○	oxytocin
[13] Systematic review	1221 women 2 RCTs in this analysis	**Need for additional therapeutic uterotonics** 54/591 (9%) with oxytocin after expectant management of third stage of labour 93/630 (15%) with expectant management alone	RR 0.66 95% CI 0.48 to 0.90	●○○	oxytocin after expectant management

No data from the following reference on this outcome. [14]

Need for additional surgical treatment

Compared with placebo/no intervention Oxytocin (given at various stages of delivery) may be no more effective than placebo or no intervention at reducing the need for manual removal of the placenta (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[13] Systematic review	2243 women 4 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Manual removal of the placenta** 51/1107 (5%) with oxytocin 43/1136 (4%) with placebo/no intervention	RR 1.17 95% CI 0.79 to 1.73	⟷	Not significant
[14] RCT	130 women in Tunisia expecting single, uncomplicated, full-term vaginal deliveries	**Need for manual removal of the placenta** 1/65 (1.5%) with oxytocin (5 IU at time of delivery) 1/65 (1.5%) with no oxytocin All women received immediate cord clamping and controlled cord traction	Significance not assessed		

Mortality

No data from the following reference on this outcome. [13] [14]

Maternal morbidity

No data from the following reference on this outcome. [13] [14]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] Systematic review	52 women Data from 1 RCT	**Nausea** 0/28 (0%) with oxytocin 1/24 (4%) with placebo/no intervention	RR 0.29 95% CI 0.01 to 6.74	⟷	Not significant

No data from the following reference on this outcome. [14]

Oxytocin versus ergot compounds:

We found one systematic review (search date 2004; see further information on studies for details of RCTs identified by the review). [13] We also found two additional RCTs [15] [16] and two subsequent RCTs [17] [18] comparing oxytocin versus ergometrine.

Postpartum haemorrhage

Compared with ergot compounds Oxytocin and ergot alkaloids may be equally effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL, or of at least 1000 mL) and at reducing volume of blood loss and need for transfusion (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[13] Systematic review	1746 women 3 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Severe postpartum haemorrhage** 20/908 (2%) with oxytocin 27/838 (3%) with ergometrine	RR 0.99 95% CI 0.56 to 1.74	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Blood loss >1000 mL** 0.65% with im oxytocin (10 IU) 0.89% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[13] Systematic review	2719 women 5 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Postpartum haemorrhage** 88/1383 (6%) with oxytocin 127/1336 (10%) with ergometrine	RR 0.90 95% CI 0.70 to 1.16	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Blood loss >500 mL** 2% with im oxytocin (10 IU) 3% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[17] RCT	600 women in Nigeria	**Blood loss >500 mL** 12/297 (4%) with oxytocin (10 IU iv) at delivery of anterior shoulder 18/303 (6%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P = 0.54	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[13] Systematic review	1373 women 2 RCTs in this analysis	**Mean blood loss** with oxytocin with ergometrine Absolute results not reported	Mean difference –29 mL 95% CI –69 mL to +1 mL	⟷	Not significant
[15] RCT	88 primigravid women of unspecified risk with vertex presentation in the UK	**Mean blood loss** 208 mL with oxytocin (10 IU iv) 201 mL with ergometrine (0.5 mg iv)	Significance not assessed		
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Mean blood loss** 183 mL with oxytocin (10 IU im) 188 mL with ergometrine (2 mg iv)	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[17] RCT	600 women in Nigeria	**Mean estimated blood loss** 246 mL with oxytocin (10 IU iv) at delivery of anterior shoulder 247 mL with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P = 0.94	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Mean blood loss , third and fourth stages of labour** 154.7 mL with iv oxytocin (5 IU) 223.5 mL with iv methylergometrine (200 micrograms) 96 mL with sublingual misoprostol (600 micrograms) 126 mL with sublingual misoprostol (400 micrograms)	P <0.01 for sublingual misoprostol 600 micrograms *v* any other intervention	○○○	sublingual misoprostol 600 micrograms
Blood transfusion					
[13] Systematic review	224 women Data from 1 RCT	**Need for blood transfusion** 2/78 (3%) with oxytocin 1/146 (1%) with ergometrine	RR 3.74 95% CI 0.34 to 40.64	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Need for blood transfusion** 0.32% with im oxytocin (10 IU) 0.44% with iv ergometrine (2 mg)	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for blood transfusion** 0/75 (0%) with oxytocin (5 IU iv) 3/75 (4%) with methylergometrine (200 micrograms iv) 0/75 (0%) with misoprostol (600 micrograms) 0/75 (0%) with misoprostol (400 micrograms)	Significance not assessed		

Need for additional medical treatment

Compared with ergot compounds Oxytocin and ergot compounds seem equally effective at reducing the need for additional medical treatment of postpartum haemorrhage (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[13] Systematic review	984 women 3 RCTs in this analysis	**Need for additional medical treatment** 35/557 (6%) with oxytocin 46/651 (7%) with ergometrine	RR 1.02 95% CI 0.67 to 1.55	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Need for use of additional oxytocic agents** 6% with im oxytocin (10 IU) 8% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[17] RCT	600 women in Nigeria	**Proportion of women needing additional oxytocic agent** 18/297 (6%) with oxytocin (10 IU iv) at delivery of anterior shoulder 30/303 (10%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P = 0.32	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for additional oxytocics** 2/75 (3%) with oxytocin (5 IU iv) 11/75 (15%) with methylergometrine (200 micrograms iv) 0/75 (0%) with misoprostol (600 micrograms) 2/75 (3%) with misoprostol (400 micrograms)	Significance not assessed		

No data from the following reference on this outcome. [15]

Need for additional surgical treatment

Compared with ergot compounds We don't know how oxytocin and ergometrine compare at reducing the need for manual removal of the placenta or the risk of retained placenta (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[13] Systematic review	1747 women 2 RCTs in this analysis 1 quasi-RCT included in meta-analysis	**Need for manual removal of placenta** 66/908 (7%) with oxytocin 70/838 (8%) with ergometrine	RR 0.57 95% CI 0.41 to 0.79	●○○	oxytocin
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Proportion of women with retained placenta** 0.8% with im oxytocin (10 IU) 0.7% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed P value not reported	⟷	Not significant
[17] RCT	600 women in Nigeria	**Need for manual removal of the placenta** 12/297 (4%) with oxytocin (10 IU iv) at delivery of anterior shoulder	P = 0.37	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		21/303 (7%) with ergometrine (0.25 mg) at delivery of anterior shoulder			

No data from the following reference on this outcome. [18]

Mortality

No data from the following reference on this outcome. [13] [15] [16] [17] [18]

Maternal morbidity

No data from the following reference on this outcome. [13] [15] [16] [17] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[15] RCT	88 primigravid women of unspecified risk with vertex presentation in the UK	**Nausea** 0/44 (0%) with iv oxytocin (10 IU) 6/44 (14%) with iv ergometrine (2 mg)	P <0.01	○○○	oxytocin
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Nausea** 2% with im oxytocin (10 IU) 1% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Vomiting** 0.3% with im oxytocin (10 IU) 0.4% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed	⟷	Not significant
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Diarrhoea** 0% with im oxytocin (10 IU) 0.3% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed	⟷	Not significant
[17] RCT	600 women in Nigeria	**Nausea** 15/297 (5%) with oxytocin (10 IU iv) at delivery of anterior shoulder 132/303 (44%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P <0.001	○○○	
[17] RCT	600 women in Nigeria	**Vomiting** 12/297 (4%) with oxytocin (10 IU iv) at delivery of anterior shoulder	P <0.001	○○○	

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		132/303 (44%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder			
Shivering					
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Shivering** 2% with im oxytocin (10 IU) 4% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed	⟷	Not significant
Headache					
[16] RCT **3-armed trial**	2023 women in Velore, India The remaining arm evaluated oral misoprostol	**Headache** 0.2% with im oxytocin (10 IU) 0.3% with iv ergometrine (2 mg) Absolute numbers not reported	Difference among groups reported as not significant; significance of between-group difference not assessed	⟷	Not significant
[17] RCT	600 women in Nigeria	**Headache** 0/297 (0%) with oxytocin (10 IU iv) at delivery of anterior shoulder 54/303 (18%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P <0.001	○○○	
Other adverse effects					
[13] Systematic review	150 women Data from 1 RCT	**Postpartum hypertension (defined as diastolic blood pressure >100 mmHg)** 4/50 (8%) with oxytocin 15/100 (15%) with ergometrine	RR 0.53 95% CI 0.19 to 1.52	⟷	Not significant
[17]	600 women in Nigeria	**Postpartum elevated blood pressure** 0/297 (0%) with oxytocin (10 IU iv) at delivery of anterior shoulder 54/303 (18%) with ergometrine (0.25 mg iv) at delivery of anterior shoulder	P <0.001	○○○	
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Increase in blood pressure** no data with oxytocin (5 IU iv) 58/75 (77%) with methylergometrine (200 micrograms iv) no data with misoprostol (600 micrograms) no data with misoprostol (400 micrograms)	Despite increase in blood pressure in women receiving methylergometrine, blood pressure remained lower than 150 mmHg systolic Significance not assessed		

Oxytocin versus oxytocin plus ergometrine combinations:

See option on oxytocin plus ergometrine combinations, p 34 .

Oxytocin versus oral misoprostol:

See option on oral misoprostol, p 61 .

Oxytocin versus sublingual misoprostol:
See option on sublingual misoprostol, p 44 .

Oxytocin versus rectal misoprostol:
See option on rectal misoprostol, p 93 .

Oxytocin versus prostaglandin E2 compounds:
See option on prostaglandin E2 compounds, p 41

Further information on studies

[13] **Oxytocin versus placebo/no intervention** The systematic review identified 5 RCTs and two quasi-RCTs comparing oxytocin versus placebo or no intervention, with oxytocin given by different routes (im in 2 RCTs and 1 quasi-randomised trial; iv in 3 RCTs and 1 quasi-randomised trial) and in a variety of doses (ranging from 3–10 IU). In two RCTs, oxytocin was used in conjunction with expectant management, in one trial with active management, and in the other trials the context was not defined. Two trials were in the US, three were in Europe (Sweden, France, and the Netherlands), and one was in Singapore. Two studies specified that the participants were low risk; the others did not specify. **Oxytocin versus ergot compounds** The review identified 5 RCTs and one quasi-randomised trial comparing oxytocin versus ergot compounds, with oxytocin given at various doses (2–10 IU) and by different modes of administration (im in 1 RCT; iv in 3 RCTs and 1 quasi-randomised trial; combined im plus iv routes in 1 RCT). Two ergot alkaloids (ergometrine and methylergonovine maleate, used in at least 4 different doses ranging from 0.2–4 mg) were assessed. Three RCTs were in the US, two were in Europe (the Netherlands and Sweden), and one was in Singapore. One specified that the women were low-risk, 4 did not specify, and one had no exclusion criteria.

Comment: The search for the Cochrane review assessing oxytocin versus placebo [13] was updated in 2009 and the results of the search were added to the awaiting classification section of the review.

Clinical guide:
Oxytocin, either alone or in combination with ergometrine, should be used for the prevention of postpartum haemorrhage. Oxytocin by itself may be preferable to the combination with ergot compounds, because differences in efficacy are likely to be small if any, and oxytocin alone seems to have fewer adverse effects. Both drugs are inexpensive and can be given im, making them useful in any resource setting. One limitation is that oxytocics, and especially ergometrine, deteriorate rapidly in tropical conditions.

OPTION CARBOPROST INJECTION

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Carboprost may be as effective as oxytocin and ergot compounds, but has been associated with unacceptable gastrointestinal effects, particularly diarrhoea and nausea.
- We found no direct information from RCTs about the effects of carboprost injection compared with no active treatment or no treatment in women with postpartum haemorrhage.

Benefits and harms

Carboprost injection versus placebo/no intervention:
We found no systematic review or RCTs.

Carboprost injection versus ergot compounds:

We found one systematic review (search date 2007), [19] which identified two RCTs comparing carboprost injection versus ergot compounds. [20] [21] We also found one additional RCT [22] and two subsequent RCTs. [23] [24]

Postpartum haemorrhage

Carboprost injection compared with ergot compounds Carboprost and methylergometrine seem equally effective at reducing the proportion of women with postpartum haemorrhage (defined as blood loss of at least 500 mL); however, carboprost seems more effective at reducing blood loss in 3rd and 4th stage labour. Carboprost and methylergometrine are equally effective at improving other measures of blood loss (volume of blood loss and haemoglobin and haematocrit levels) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[20] RCT	150 low-risk women in Egypt In review [19]	**Postpartum haemorrhage (blood loss of at least 500 mL)** 0% with carboprost trometamol (250 micrograms im) 0% with methylergometrine (0.2 mg iv)	Significance not assessed		
[21] RCT	80 women with at least 1 risk factor for postpartum haemorrhage, delivering after 28 weeks' gestation In review [19]	**Postpartum haemorrhage** 2/40 (5%) with carboprost (250 micrograms im) 3/40 (8%) with methylergometrine (0.2 mg iv)	P = 1.0	⟷	Not significant
[22] RCT	215 women	**Postpartum haemorrhage** 5/107 (5%) with carboprost tromethamine (250 micrograms im) 7/108 (7%) with methylergometrine (iv dose not reported)	RR 0.72 95% CI 0.24 to 2.20	⟷	Not significant
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Postpartum haemorrhage** 0/50 (0%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 2/50 (4%) with methylergometrine (0.2 mg) after placental delivery See further information on studies for definition of outcome	Significance not assessed.		
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Postpartum haemorrhage (blood loss of at least 500 mL)** 13/67 (19%) with carboprost tromethamine (250 micrograms im) 12/67 (18%) with methylergometrine (0.2 mg iv) 8/66 (12%) with misoprostol (400 micrograms sublingually)	P = 0.49 among all 3 groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[21] RCT	80 women with at least 1 risk factor for postpartum haemorrhage, delivering after 28 weeks' gestation In review [19]	**Blood loss in third stage labour** 113 mL with carboprost (250 micrograms im) 202 mL with methylergometrine (0.2 mg iv)	P <0.001	○○○	carboprost
[21] RCT	80 women with at least 1 risk factor for postpartum haemorrhage, delivering after 28 weeks' gestation In review [19]	**Blood loss in fourth stage labour** 47 mL with carboprost (250 micrograms im) 67 mL with methylergometrine (0.2 mg iv)	P <0.001	○○○	carboprost
[22] RCT	215 women	**Mean blood loss** 235.7 mL with carboprost tromethamine (250 micrograms) 214.1 mL with methylergometrine (iv dose not reported)	Mean difference +21.6 mL 95% CI –6.5 mL to +49.8 mL	⟷	Not significant
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Mean blood loss** 96 mL with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 250 mL with methylergometrine (0.2 mg) after placental delivery	Significance not assessed.		
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Median blood loss** 227 mL with carboprost tromethamine (250 micrograms im) 194 mL with methylergometrine (0.2 mg iv) 223.5 mL with misoprostol (400 micrograms sublingually)	P = 0.57 among all 3 groups	⟷	Not significant
Blood transfusion					
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Blood transfusion** 0/50 (0%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 2/50 (4%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed.		
Postpartum haemoglobin/haematocrit level					
[22] RCT	215 women	**Postpartum haemoglobin or haematocrit levels** with carboprost tromethamine (250 micrograms) with methylergometrine (iv dose not reported) Absolute numbers not reported	Reported as not significant P value not reported	⟷	Not significant

Mortality

No data from the following reference on this outcome. [19] [20] [21] [22] [23] [24]

Maternal morbidity

No data from the following reference on this outcome. [19] [20] [21] [22] [23] [24]

Need for additional medical treatment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional oxytocics					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Need for additional oxytocics** 9/67 (13%) with carboprost tromethamine (250 micrograms im) 14/67 (21%) with methylergometrine (0.2 mg iv) 9/66 (14%) with misoprostol (400 micrograms sublingually)	P = 0.41 among all 3 groups	⟷	Not significant

No data from the following reference on this outcome. [19] [20] [21] [22] [23]

Need for additional surgical treatment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Retained placenta					
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Retained placenta** 0/50 (0%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 0/50 (0%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed		

No data from the following reference on this outcome. [19] [20] [21] [22] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[20] RCT	150 low-risk women in Egypt In review [19]	**Vomiting** 16% with carboprost trometamol (250 micrograms im) 1% with methylergometrine (0.2 mg iv) Absolute numbers not reported	RR 12.7 95% CI 1.7 to 94.9	●●●	methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Vomiting** 1/50 (2%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 2/50 (4%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed.		
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Nausea** 3/50 (6%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 0/50 (0%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed.		
[20] RCT	150 low-risk women in Egypt In review [19]	**Diarrhoea** 3% with carboprost trometamol (250 micrograms im) 0% with methylergometrine (0.2 mg iv)	RR 5.27 95% CI 0.26 to 108.00	⟷	Not significant
[21] RCT	80 women with at least 1 risk factor for postpartum haemorrhage, delivering after 28 weeks' gestation In review [19]	**Diarrhoea** 17% with carboprost (250 micrograms im) 0% with methylergometrine (0.2 mg iv)	P = 0.01	○○○	methylergometrine
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Diarrhoea** 2 (4%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 0 (0%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed.		
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Nausea** 2/67 (3%) with carboprost tromethamine (250 micrograms im) 1/67 (1%) with methylergometrine (0.2 mg iv) 6/66 (9%) with misoprostol (400 micrograms sublingually)	P = 0.10 among all 3 groups	⟷	Not significant
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Vomiting** 1/67 (1%) with carboprost tromethamine (250 micrograms im) 1/67 (1%) with methylergometrine (0.2 mg iv) 8/66 (12%) with misoprostol (400 micrograms sublingually)	P = 0.006 among all 3 groups	○○○	carboprost or methylergometrine
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Diarrhoea** 1/66 (2%) with misoprostol (400 micrograms sublingually) 7/67 (10%) with carboprost tromethamine (250 micrograms im)	P = 0.004 among all 3 groups	○○○	sublingual misoprostol or methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/67 (0%) with methylergometrine (0.2 mg iv)			
Abdominal pain					
[20] RCT	150 low-risk women in Egypt In review [19]	**Abdominal pain** 8% with carboprost trometamol (250 micrograms im) 0% with methylergometrine (0.2 mg iv) Absolute numbers not reported	RR 13.70 95% CI 0.79 to 239.0	○○○	
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Abdominal pain** 2/67 (3%) with carboprost tromethamine (250 micrograms im) 0/67 (0%) with methylergometrine (0.2 mg iv) 2/66 (3%) with misoprostol (400 micrograms sublingually)	P = 0.47 among all 3 groups	⟷	Not significant
Raised blood pressure					
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Raised blood pressure** 0/50 (0%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 5/50 (10%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed		
Pyrexia					
[23] RCT	100 women having vaginal deliveries at a hospital in India	**Pyrexia** 1/50 (2%) with 15-methyl prostaglandin F2-alpha (125 micrograms) at time of delivery of anterior shoulder 0/50 (0%) with methylergometrine (0.2 mg) after placental delivery	Significance not assessed		

Carboprost injection versus oxytocin plus ergometrine:

We found one systematic review (search date 2007) [19] and one additional RCT. [25]

Postpartum haemorrhage

Carboprost injection compared with oxytocin plus ergometrine combination We don't know how carboprost and a fixed combination of oxytocin and ergometrine compare at reducing blood loss (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[26] RCT	112 women In review [19]	**Blood loss** with 15-methyl prostaglandin F2-alpha (125 micrograms im) with oxytocin (0.5 mg) plus ergometrine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[25] RCT	529 women	**Blood loss** 43/263 (16%) with carboprost (250 micrograms im) 30/266 (11%) with oxytocin plus ergometrine	RR 1.45 95% CI 0.94 to 2.24 Results from interim analysis: see further information on studies for full details	⟷	Not significant
Postpartum haemoglobin/haematocrit level					
[26] RCT	112 women In review [19]	**Haemoglobin change** with 15-methyl prostaglandin F2-alpha (125 micrograms im) with oxytocin (0.5 mg) plus ergometrine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

Need for additional medical treatment

Carboprost injection compared with oxytocin plus ergometrine combination We don't know how carboprost and a fixed combination of oxytocin and ergometrine compare at reducing the need for additional oxytocic agents (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatments					
[26] RCT	112 women In review [19]	**Need for additional oxytocic agents** with 15-methyl prostaglandin F2-alpha (125 micrograms im) with oxytocin (0.5 mg) plus ergometrine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [25]

Need for additional surgical treatment

Carboprost injection compared with oxytocin plus ergometrine combination We don't know how carboprost and a fixed combination of oxytocin and ergometrine compare at reducing the need for manual removal of the placenta (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[26] RCT	112 women In review [19]	**Manual removal of the placenta** with 15-methyl prostaglandin F2-alpha (125 micrograms im) with oxytocin (0.5 mg) plus ergometrine Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [25]

Mortality

No data from the following reference on this outcome. [25] [26]

Maternal morbidity

No data from the following reference on this outcome. [25] [26]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[25] RCT	529 women	**Nausea** 4% with carboprost (250 micrograms im) 1% with oxytocin plus ergometrine Study terminated early because of GI adverse effects with carboprost	Significance of interim results not assessed		
[26] RCT	112 women In review [19]	**Diarrhoea** 16/54 (30%) with carboprost (250 micrograms im) 1/58 (2%) with oxytocin plus ergometrine	P <0.005	○○○	oxytocin plus ergometrine
[25] RCT	529 women	**Diarrhoea** 21% with carboprost (250 micrograms im) 1% with oxytocin plus ergometrine Study terminated early because of GI adverse effects with carboprost	Significance of interim results not assessed		
[25] RCT	529 women	**All gastrointestinal adverse effects** 27% with carboprost (250 micrograms im) 6% with oxytocin plus ergometrine Study terminated early because of GI adverse effects with carboprost	Significance of interim results not assessed		

Carboprost injection versus sublingual misoprostol:

See option on sublingual misoprostol, p 44 .

Carboprost injections versus rectal misoprostol:

See option on rectal misoprostol, p 93 .

Further information on studies

[25] The RCT was terminated early at the time of interim analysis because of unacceptable gastrointestinal adverse effects in the prostaglandin group. At the time of termination, there was no suggestion of a difference in effectiveness between the study groups.

[23] The RCT reports on the number of women with postpartum haemorrhage. It does not state how much blood loss was defined as PPH, but it does say that women with PPH needed blood transfusion.

Comment: **Clinical guide:**
Data on injectable carboprost are limited, but it is clearly no better than oxytocin, ergot compounds, or combinations, and has more adverse effects.

OPTION ERGOT COMPOUNDS (ERGOMETRINE/METHYLERGOTAMINE)

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Ergot compounds seem as effective as oxytocin, but are also associated with adverse effects including nausea, placenta retention, and hypertension.
- Prostaglandin treatments vary in their efficacy, but are all associated with adverse effects.

Benefits and harms

Ergot compounds versus placebo/no intervention:

We found one systematic review (search date 2008, 6 RCTs, 3941 women in resource-rich countries) comparing ergot compounds versus placebo or no intervention. [27] The RCTs included in the review used a variety of doses and routes of administration of ergometrine or methylergonovine (see further information on studies for full details).

Postpartum haemorrhage

Compared with placebo/no intervention Iv and im ergot compounds are more effective than placebo or no intervention at reducing postpartum haemorrhage (defined as blood loss of 500 mL or of at least 1000 mL) and at improving postpartum haemoglobin levels. Iv or im ergot compounds seem no more effective at reducing the need for transfusion (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[27] Systematic review	1429 women Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 0.09 95% CI 0.01 to 0.72	●●●	ergot alkaloids
[27] Systematic review	3409 women 3 RCTs in this analysis	**Postpartum haemorrhage (blood loss of at least 500 mL)** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 0.38 95% CI 0.21 to 0.69	●●○	ergot alkaloids
Blood loss (volume)					
[27] Systematic review	2429 women 2 RCTs in this analysis	**Mean blood loss** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	WMD –83.0 mL 95% CI –99.4 mL to –66.7 mL	○○○	ergot alkaloids

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood transfusion					
[27] Systematic review	1579 women 2 RCTs in this analysis	**Need for blood transfusion** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 0.34 95% CI 0.05 to 2.16	⟷	Not significant
Postpartum haemoglobin/haematocrit level					
[27] Systematic review	1429 women Data from 1 RCT	**Postpartum haemoglobin <10 g/dL** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 0.30 95% CI 0.14 to 0.67	●●○	ergot alkaloids
[27] Systematic review	1429 women Data from 1 RCT	**Mean haemoglobin , 48–72 hours postpartum** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	WMD 0.50 g/dL 95% CI 0.38 g/dL to 0.62 g/dL	○○○	ergot alkaloids

Need for additional medical treatment

Compared with placebo/no intervention Ergot compounds seem more effective than placebo or no intervention at reducing the need for additional uterotonics (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[27] Systematic review	2409 women 2 RCTs in this analysis	**Need for additional uterotonics** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 0.25 95% CI 0.10 to 0.66	●●○	ergot alkaloids

Need for additional surgical treatment

Compared with placebo/no intervention Iv or im ergot alkaloids seem no more effective than placebo or no intervention at reducing the need for manual removal of the retained placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[27] Systematic review	1429 women 2 RCTs in this analysis	**Risk of retained placenta or need for manual removal of placenta** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 3.75 95% CI 0.14 to 99.7	⟷	Not significant

Mortality

No data from the following reference on this outcome. [27]

Maternal morbidity

No data from the following reference on this outcome. [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[27] Systematic review	1579 women 2 RCTs in this analysis	**Nausea** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 8.63 95% CI 0.26 to 284.55	⟷	Not significant
[27] Systematic review	1579 women 2 RCTs in this analysis	**Vomiting** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 11.81 95% CI 1.78 to 78.28	●●●	placebo/no treatment
Headache					
[27] Systematic review	1579 women 2 RCTs in this analysis	**Headache** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 3.93 95% CI 0.51 to 30.50	⟷	Not significant
Other adverse effects					
[27] Systematic review	1559 women 3 RCTs in this analysis	**Elevated blood pressure** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 2.60 95% CI 1.03 to 6.57	●●○	placebo/no treatment
[27] Systematic review	1429 women Data from 1 RCT	**Additional pain after birth** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 2.53 95% CI 1.34 to 4.78	●●○	placebo/no treatment
[27] Systematic review	1579 women 2 RCTs in this analysis	**Eclampsia** with iv or im ergot alkaloids with placebo/no treatment Absolute results not reported	RR 3.34 95% CI 0.38 to 29.43	⟷	Not significant

Ergot compounds versus oxytocin:

See option on oxytocin, p 15 .

Ergot compounds versus oxytocin plus ergometrine combinations:

See option on oxytocin plus ergometrine combinations, p 34 .

Ergot compounds versus oral misoprostol:

See option on oral misoprostol, p 61 .

Ergot compounds versus sublingual misoprostol:

See option on sublingual misoprostol, p 44 .

Ergot compounds versus carboprost:

See option on carboprost, p 23 .

Further information on studies

[27] Four RCTs administered the drug iv, one RCT im, and one RCT orally. The iv and im doses ranged from 0.2 mg to 0.5 mg. The oral dose was 0.4 mg.

Comment:

Clinical guide:
Ergot compounds are clearly effective in preventing postpartum haemorrhage but are associated with significant adverse effects. They may be administered iv or im, but there is no supportive evidence for oral administration being effective. They may be administered in combination with oxytocin (syntometrine). They should be administered when no other uterotonic is available, but given the adverse-effect profile, and similar effectiveness to oxytocin, oxytocin is the preferred agent when available.

OPTION OXYTOCIN PLUS ERGOMETRINE

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- A combination of oxytocin plus ergometrine may be slightly more effective than oxytocin alone, although there are more adverse effects.

Benefits and harms

Oxytocin plus ergometrine versus ergot compounds alone:

We found one systematic review (search date 2004; 4 RCTs and 1 controlled trial including a total of 2891 women) comparing oxytocin plus ergometrine combinations versus ergot alkaloids alone. [13]

Postpartum haemorrhage

Compared with ergot compounds alone Oxytocin plus ergometrine combinations and ergot compounds alone seem equally effective at reducing postpartum haemorrhage (defined as blood loss of 500 mL or 1000 mL or greater) and at reducing the need for transfusion (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[13] Systematic review	1120 women Data from 1 controlled trial	**Severe postpartum haemorrhage (defined as estimated blood loss >1000 mL)** 5/560 (0.9%) with oxytocin plus ergometrine	RR 1.67 95% CI 0.40 to 6.94	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		3/560 (0.5%) with ergot compounds See further information on studies for details of regimens used in identified RCTs			
[13] Systematic review	2891 women 5 RCTs in this analysis 1 controlled trial included in meta-analysis	**Postpartum haemorrhage (defined as estimated blood loss >500 mL)** 66/1427 (5%) with oxytocin plus ergometrine 52/1464 (4%) with ergot compounds See further information on studies for details of regimens used in identified RCTs	RR 1.29 95% CI 0.90 to 1.84	⟷	Not significant
Blood transfusion					
[13] Systematic review	1120 women Data from 1 controlled trial	**Need for blood transfusion** 5/560 (0.9%) with oxytocin plus ergometrine 7/560 (1%) with ergot compounds See further information on studies for details of regimens used in identified RCTs	RR 0.71 95% CI 0.23 to 2.24	⟷	Not significant

Need for additional surgical treatment

Compared with ergot compounds alone Oxytocin plus ergometrine combinations and ergot compounds alone seem equally effective at reducing the need for manual removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[13] Systematic review	1927 women 2 RCTs in this analysis 1 controlled trial included in meta-analysis	**Need for manual removal of placenta** 13/951 (1%) with oxytocin plus ergometrine 13/976 (1%) with ergot compounds See further information on studies for details of regimens used in identified RCTs	RR 1.02 95% CI 0.48 to 2.20	⟷	Not significant

Mortality

No data from the following reference on this outcome. [13]

Maternal morbidity

No data from the following reference on this outcome. [13]

Need for additional medical treatment

No data from the following reference on this outcome. [13]

Adverse effects

No data from the following reference on this outcome. [13]

Oxytocin plus ergometrine versus oxytocin alone:

We found one systematic review (search date 2007; 5 RCTs and 1 controlled trial including a total of 9332 women) comparing oxytocin versus combined oxytocin plus ergot alkaloid preparations. [28] Various doses were used in the identified RCTs (see further information on studies for full details). We also found one subsequent RCT. [29]

Postpartum haemorrhage

Compared with oxytocin alone Oxytocin plus ergometrine combinations seem more effective than oxytocin alone at reducing postpartum haemorrhage (defined as blood loss of 500 mL or greater), but seem no more effective than oxytocin alone at reducing the risk of severe postpartum haemorrhage (defined as blood loss of 1000 mL or greater) or at reducing the need for blood transfusion (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[28] Systematic review	9332 women 6 RCTs in this analysis 1 controlled trial included in meta-analysis	**Severe postpartum haemorrhage (defined as blood loss of 1000 mL or greater)** 86/3972 (2%) with oxytocin plus ergometrine 111/3982 (3%) with oxytocin (any dose) All women had active management of the third stage of labour	OR 0.78 95% CI 0.58 to 1.03	⟷	Not significant
[28] Systematic review	9332 women 6 RCTs in this analysis 1 controlled trial included in meta-analysis	**Postpartum haemorrhage (defined as blood loss of 500 mL or greater)** 392/4661 (8%) with oxytocin plus ergometrine 469/4671 (10%) with oxytocin (any dose) All women had active management of the third stage of labour	OR 0.82 95% CI 0.71 to 0.95	●○○	oxytocin plus ergometrine
[28] Systematic review	1839 women 2 RCTs in this analysis 1 controlled trial included in meta-analysis	**Postpartum haemorrhage (defined as blood loss of 500 mL or greater)** 11/919 (1%) with oxytocin plus ergometrine 26/920 (3%) with oxytocin (5 IU) All women had active management of the third stage of labour	OR 0.43 95% CI 0.23 to 0.83	●●○	oxytocin plus ergometrine
[28] Systematic review	7493 women 4 RCTs in this analysis	**Postpartum haemorrhage (defined as blood loss of 500 mL or greater)**	OR 0.85 95% CI 0.73 to 0.98	●○○	oxytocin plus ergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		372/3472 (10%) with oxytocin plus ergometrine 432/3751 (12%) with oxytocin (10 IU) All women had active management of the third stage of labour			
[29] RCT	686 women in Saudi Arabia	**Postpartum haemorrhage (defined as blood loss of 500 mL or greater up to 1000 mL)** 8/340 (2%) with oxytocin plus ergometrine (1 mL im) 9/346 (3%) with oxytocin (10 IU)	RR 0.90 95% CI 0.35 to 2.32	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Postpartum haemorrhage (defined as blood loss of greater than 1000 mL)** 6/340 (1.8%) with oxytocin plus ergometrine (1 mL im) 8/346 (2.3%) with oxytocin (10 IU)	RR 0.76 95% CI 0.27 to 2.18	⟷	Not significant
Blood loss during delivery					
[29] RCT	686 women in Saudi Arabia	**Mean blood loss during delivery** 246 mL with oxytocin plus ergometrine (1 mL im) 248 mL with oxytocin (10 IU)	Mean difference +2.68 95% CI –16.82 to +22.17	⟷	Not significant
[29] RCT	Women in Saudi Arabia with a parity of 0; number not reported Subgroup analysis	**Mean blood loss in women with parity of 0** 242 mL with oxytocin plus ergometrine (1 mL im) 241 mL with oxytocin (10 IU)	P = 0.96 The number of women in this RCT with parity 0 was not reported	⟷	Not significant
[29] RCT	Women in Saudi Arabia with a parity of 1 to 4; number not reported Subgroup analysis	**Mean blood loss in women with parity of 1 to 4** 265 mL with oxytocin plus ergometrine (1 mL im) 253 mL with oxytocin (10 IU)	P = 0.38 The number of women in this RCT with parity 1 to 4 was not reported	⟷	Not significant
[29] RCT	Women in Saudi Arabia with a parity of 5; number not reported Subgroup analysis	**Mean blood loss in women with parity of 5 or more** 210 mL with oxytocin plus ergometrine (1 mL im) 244 mL with oxytocin (10 IU)	P = 0.06 The number of women in the RCT with a parity of 5 or more was not reported	○○○	oxytocin plus ergometrine
Blood transfusion					
[28] Systematic review	7482 women 4 RCTs in this analysis	**Need for blood transfusion** 49/3725 (1%) with oxytocin plus ergometrine 36/3747 (1%) with oxytocin (10 IU) All women had active management of the third stage of labour	OR 1.37 95% CI 0.89 to 2.10	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Proportion of women needing blood transfusion** 6/340 (2%) with oxytocin plus ergometrine (1 mL im)	RR 3.05 95% CI 0.62 to 15.02	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2/346 (1%) with oxytocin (10 IU)			

Need for additional medical treatment

Compared with oxytocin alone We don't know how oxytocin plus ergometrine combinations and oxytocin alone compare at reducing the need for additional medical treatment of postpartum haemorrhage (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[28] Systematic review	5465 women 3 RCTs in this analysis	**Need for additional medical treatment** 397/2726 (15%) with oxytocin plus ergometrine 466/2739 (17%) with oxytocin (10 IU) All women had active management of the third stage of labour	OR 0.83 95% CI 0.72 to 0.96 Significant statistical heterogeneity among RCTs (no further data reported) Results not significant with random effects model (OR 0.87, 95% CI 0.58 to 1.32)	●○○	oxytocin plus ergometrine
[29] RCT	686 women in Saudi Arabia	**Need for repeat oxytocin administration** 35/340 (10.3%) with oxytocin plus ergometrine (1 mL im) 34/346 (9.8%) with oxytocin (10 IU)	RR 1.05 95% CI 0.67 to 1.64	⟷	Not significant

Need for additional surgical treatment

Compared with oxytocin alone Oxytocin plus ergometrine combinations and oxytocin alone are equally effective at reducing the need for manual removal of the placenta (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of placenta					
[28] Systematic review	9332 women 6 RCTs in this analysis 1 controlled trial included in meta-analysis	**Need for manual removal of placenta** 130/4661 (3%) with oxytocin plus ergometrine 127/4671 (3%) with oxytocin (10 IU) All women had active management of the third stage of labour	OR 1.03 95% CI 0.80 to 1.33	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Need for manual removal of the placenta** 0/340 (0%) with oxytocin plus ergometrine (1 mL im) 1/346 (0.3%) with oxytocin (10 IU)	P = 1.00	⟷	Not significant

Mortality

No data from the following reference on this outcome. [28] [29]

Maternal morbidity

No data from the following reference on this outcome. [28] [29]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[28] Systematic review	5458 women 3 RCTs in this analysis	**Nausea** 487/2721 (18%) with oxytocin plus ergometrine 128/2737 (5%) with oxytocin All women had active management of the third stage of labour	OR 4.07 95% CI 3.43 to 4.84	●●○	oxytocin alone
[28] Systematic review	5458 women 3 RCTs in this analysis	**Vomiting** 373/2721 (14%) with oxytocin plus ergometrine 66/2737 (2%) with oxytocin All women had active management of the third stage of labour	OR 4.92 95% CI 4.03 to 6.00	●●○	oxytocin alone
[28] Systematic review	7477 women 4 RCTs in this analysis	**Nausea and vomiting combined** 874/3737 (23%) with oxytocin plus ergometrine 198/3749 (5%) with oxytocin All women had active management of the third stage of labour	OR 5.71 95% CI 4.97 to 6.57	●●●	oxytocin alone
[29] RCT	686 women in Saudi Arabia	**Nausea** 12/340 (4%) with oxytocin plus ergometrine (1 mL im) 10/346 (3%) with oxytocin (10 IU)	RR 1.22 95% CI 0.53 to 2.79	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Vomiting** 4/340 (1.1%) with oxytocin plus ergometrine (1 mL im) 1/346 (0.3%) with oxytocin (10 IU)	RR 4.07 95% CI 0.46 to 36.23	⟷	Not significant
Increase in blood pressure					
[28] Systematic review	unclear 3 RCTs in this analysis	**Increase in diastolic blood pressure** with oxytocin plus ergometrine with oxytocin Absolute results not reported All women had active management of the third stage of labour	OR 2.81 95% CI 1.17 to 6.73	●●○	oxytocin alone
[29] RCT	686 women in Saudi Arabia	**Systolic blood pressure >140 mmHg , immediately after delivery** 24/340 (7%) with oxytocin plus ergometrine (1 mL im)	RR 0.81 95% CI 0.49 to 1.36	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		30/346 (9%) with oxytocin (10 IU)			
[29] RCT	686 women in Saudi Arabia	**Systolic blood pressure >140 mmHg , 30 minutes after delivery** 9/340 (3%) with oxytocin plus ergometrine (1 mL im) 12/346 (4%) with oxytocin (10 IU)	RR 0.76 95% CI 0.33 to 1.79	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Diastolic blood pressure >90 mmHg , immediately after delivery** 7/340 (2%) with oxytocin plus ergometrine (1 mL im) 10/346 (3%) with oxytocin (10 IU)	RR 0.71 95% CI 0.27 to 1.85	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Diastolic blood pressure >90 mmHg , 30 minutes after delivery** 15/340 (4%) with oxytocin plus ergometrine (1 mL im) 3/346 (1%) with oxytocin (10 IU)	RR 5.09 95% CI 1.49 to 17.42	●●●	oxytocin
Other adverse effects					
[29] RCT	686 women in Saudi Arabia	**Headache** 2/340 (0.59%) with oxytocin plus ergometrine (1 mL im) 2/346 (0.58%) with oxytocin (10 IU)	RR 1.02 95% CI 0.14 to 7.18	⟷	Not significant
[29] RCT	686 women in Saudi Arabia	**Chest pain** 2/340 (0.6%) with oxytocin plus ergometrine (1 mL im) 3/346 (0.9%) with oxytocin (10 IU)	RR 0.68 95% CI 0.11 to 4.03	⟷	Not significant

Oxytocin plus ergometrine versus carboprost:

See option on carboprost, p 23 .

Oxytocin plus ergometrine versus prostaglandin E2 compounds:

See option on prostaglandin E2 compounds, p 41 .

Oxytocin plus ergometrine versus sublingual misoprostol:

See option on sublingual misoprostol, p 44 .

Oxytocin plus ergometrine versus oral misoprostol:

See option on oral misoprostol, p 61 .

Oxytocin plus ergometrine versus rectal misoprostol:

See option on rectal misoprostol, p 93 .

Further information on studies

[13] The combination consisted of oxytocin 5 IU plus ergometrine 0.5 mg (given im in all but 1 RCT, where it was given iv), whereas the ergot comparison contained ergometrine in three RCTs, ergometrine maleate in one RCT, and methergine in one controlled trial, with doses varying from 0.1 to 0.5 mg, and administration being iv in one RCT and one controlled trial, im in one RCT, and both in two RCTs. Two studies were conducted in the UK, one in Australia, one in Singapore, and one in Finland. The review reported that two were in low-risk populations and did not specify regarding the other three.

[28] Women in the oxytocin group received doses of 5 IU (2 trials) or 10 IU (4 trials), whereas all women in the combination group received oxytocin 5 IU plus ergometrine 0.5 mg im. One study was conducted in the United Arab Emirates, one in Australia, two in Hong Kong, one in the UK, and one in Sweden. Four populations seemed to be low-risk, and two were not specified.

[29] Women in this trial received either one vial of im syntometrine (1 vial contains 1 mL of syntometrine, which is made up of 5 units of syntocinon and 0.5 mg of ergometrine) or 10 units of iv syntocinon (a synthetic form of oxytocin). The drug was administered with the delivery of the anterior shoulder of the baby in both treatment groups. Irrespective of the allocation to drug group, an additional dose of syntometrine was given if the uterus was not very well contracted or there was excessive vaginal bleeding. Grandmultiparity (a parity of 5 or more) and great-grandmultiparity (parity of 10 or more) are relatively common in Saudi Arabia. In this trial, 27% of maternities were para 5 or more, whereas in the UK the incidence of para 5 maternities is 0.7%.

Comment: **Oxytocin plus ergometrine combinations versus oxytocin:**
All 4 RCTs (7477 women) reporting elevated blood pressure as outcome gave oxytocin 10 IU in the control arm. [28] In spite of varying definitions of elevated blood pressure, and significant heterogeneity between studies, the authors still found a significant effect when applying a random-effects model.

OPTION PROSTAGLANDIN E2 COMPOUNDS

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Prostaglandin E2 compounds may be as effective as oxytocin and ergot compounds, but are associated with gastrointestinal adverse effects, such as diarrhoea.

Benefits and harms

Sulprostone injection versus placebo:

We found one systematic review (search date 2007), [19] which identified one RCT [30] comparing sulprostone injection versus placebo.

Postpartum haemorrhage

Compared with placebo Sulprostone seems no more effective than placebo at reducing postpartum haemorrhage or severe postpartum haemorrhage, defined as blood loss of >500 mL or >1000 mL, respectively (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[30] RCT **3-armed trial**	77 women in the Netherlands In review [19] The remaining arm evaluated oxytocin (5 IU)	**Severe postpartum haemorrhage (defined as estimated blood loss >1000 mL)** 1/22 (5%) with sulprostone injection (500 micrograms im)	RR 0.36 for sulprostone *v* placebo 95% CI 0.04 to 3.24	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2/24 (8%) with placebo (0.9% saline) 46 women in this analysis			
[30] RCT **3-armed trial**	77 women in the Netherlands In review [19] The remaining arm evaluated oxytocin (5 IU)	**Postpartum haemorrhage (defined as estimated blood loss >500 mL)** 5/22 (23%) with sulprostone injection (500 micrograms im) 10/24 (42%) with placebo (0.9% saline) 46 women in this analysis	RR 0.55 for sulprostone *v* placebo 95% CI 0.22 to 1.35	⟷	Not significant

Need for additional medical treatment

Compared with placebo Sulprostone seems no more effective than placebo at reducing the need for further medical treatment for postpartum haemorrhage (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[30] RCT **3-armed trial**	77 women in the Netherlands In review [19] The remaining arm evaluated oxytocin (5 IU)	**Need for medical treatment** 0/22 (0%) with sulprostone injection (500 micrograms im) 2/24 (8%) with placebo (0.9% saline) 46 women in this analysis	RR 0.22 for sulprostone *v* placebo 95% CI 0.01 to 4.29	⟷	Not significant

Mortality

No data from the following reference on this outcome. [30]

Maternal morbidity

No data from the following reference on this outcome. [30]

Need for additional surgical treatment

No data from the following reference on this outcome. [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT **3-armed trial**	77 women in the Netherlands In review [19] The remaining arm evaluated oxytocin (5 IU)	**Any adverse effect** 0/22 (0%) with sulprostone injection (500 micrograms im) 1/24 (4%) with placebo (0.9% saline) The adverse effect reported in the process group was nausea 46 women in this analysis	RR 0.36 for sulprostone *v* placebo 95% CI 0.02 to 8.46	⟷	Not significant

Sulprostone injection versus oxytocin:

We found one systematic review (search date 2007), [19] which identified one RCT comparing sulprostone injection versus oxytocin. [30]

Postpartum haemorrhage

Compared with oxytocin We don't know how sulprostone and oxytocin compare at reducing blood loss (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[30] RCT **3-armed trial**	77 women in The Netherlands In review [19] The remaining arm evaluated placebo (0.9% saline)	**Measured blood loss** 324 mL with sulprostone injection (500 micrograms im) 374 mL with oxytocin (5 IU) 51 women in this analysis	Significance not assessed		

Need for additional medical treatment

Compared with oxytocin We don't know how sulprostone and oxytocin compare at reducing the need for additional medical treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[30] RCT **3-armed trial**	77 women in the Netherlands In review [19] The remaining arm evaluated placebo (0.9% saline)	**Need for additional medical treatment** 0/22 (0%) with sulprostone injection (500 micrograms im) 0/29 (0%) with oxytocin (5 IU) 51 women in this analysis	Significance not assessed		

Need for additional surgical treatment

Compared with oxytocin We don't know how sulprostone and oxytocin compare at reducing the need for manual removal of the placenta (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[30] RCT	77 women in the Netherlands	**Need for manual removal of the placenta**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	In review [19] The remaining arm evaluated placebo (0.9% saline)	0/22 (0%) with sulprostone injection (500 micrograms im) 0/29 (0%) with oxytocin (5 IU) 51 women in this analysis			

Mortality

No data from the following reference on this outcome. [30]

Maternal morbidity

No data from the following reference on this outcome. [30]

Adverse effects

No data from the following reference on this outcome. [30]

Sulprostone injection versus oxytocin plus ergometrine:

We found one systematic review (search date 2007), [19] which identified one RCT. [31] The RCT (69 women with prior postpartum haemorrhage in the Netherlands) compared sulprostone (500 micrograms im) versus a fixed combination of oxytocin plus ergometrine. [31] The RCT found trends of decreased blood loss and transfusion with sulprostone, but the trial was terminated early when the manufacturer of the prostaglandin preparation issued a warning against im injection after receiving reports of cardiovascular complications outside the study.

Dinoprostone injections:

We found no systematic review or RCTs on the effects of dinoprostone.

Further information on studies

Comment: **Clinical guide:**
Data on injectable prostaglandins are limited, but injectable sulprostone seems no better than oxytocin, ergot compounds, or combinations, and is associated with more adverse effects. Injectable prostaglandins are not available in many resource-poor countries.

OPTION MISOPROSTOL (SUBLINGUAL)

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .

- Sublingually administered misoprostol may be more effective than placebo in preventing postpartum haemorrhage (evidenced by a single RCT).
- Sublingual misoprostol has similar effects to injected agents, but is associated with more adverse effects.

Benefits and harms

Sublingual misoprostol versus placebo/no intervention:

We found one systematic review (search date 2007), [19] which identified one RCT. [32]

Mortality

Compared with placebo/no intervention We don't know whether misoprostol administered sublingually is more effective than placebo or no intervention at reducing mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Mortality** 1 with misoprostol 0 with placebo	Significance not assessed		

Postpartum haemorrhage

Compared with placebo/no intervention Misoprostol administered sublingually seems more effective than placebo or no intervention at reducing severe postpartum haemorrhage (defined as blood loss of at least 1000 mL or 1500 mL) but no more effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Proportion of women with an estimated blood loss of at least 1500 mL** 2% with misoprostol (600 micrograms sublingually) 8% with placebo Absolute numbers not reported	RR 0.28 95% CI 0.12 to 0.64	●●○	misoprostol
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Proportion of women with an estimated blood loss of at least 1000 mL** 11% with misoprostol (600 micrograms sublingually) 17% with placebo Absolute numbers not reported	RR 0.66 95% CI 0.45 to 0.98	●○○	misoprostol
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Proportion of women with an estimated blood loss of at least 500 mL** 45% with misoprostol (600 micrograms sublingually) 51% with placebo Absolute numbers not reported	RR 0.89 95% CI 0.76 to 1.04	⟷	Not significant

Need for additional medical treatment

Compared with placebo/no intervention We don't know whether sublingual misoprostol is more effective than placebo or no intervention at reducing the need for transfer to hospital (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Need for transfer to hospital** 0.9% with misoprostol (600 micrograms sublingually) 0.9% with placebo Absolute numbers not reported	Significance not assessed		

Need for additional surgical treatment

Compared with placebo/no intervention We don't know whether sublingual misoprostol is more effective than placebo or no intervention at reducing placental retention (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Retained placental tissue** 3% with misoprostol (600 micrograms sublingually) 3% with placebo Absolute numbers not reported	Significance not assessed		

No data from the following reference on this outcome. [32]

Maternal morbidity

No data from the following reference on this outcome. [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Nausea** 2/330 (0.6%) with misoprostol (600 micrograms sublingually) 4/331 (1.2%) with placebo Absolute numbers not reported	RR 0.50 95% CI 0.09 to 2.72	⟷	Not significant
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Vomiting** 3% with misoprostol (600 micrograms sublingually) 1% with placebo Absolute numbers not reported	RR 2.51 95% CI 0.79 to 7.91	⟷	Not significant
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Diarrhoea** 3% with misoprostol (600 micrograms sublingually) 1% with placebo Absolute numbers not reported	RR 2.50 95% CI 0.79 to 7.8	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Shivering					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Shivering** 57% with misoprostol (600 micrograms sublingually) 24% with placebo Absolute numbers not reported	RR 2.43 95% CI 1.96 to 3.02	●●○	placebo
Fever					
[32] RCT	661 women delivering in local health centres in Guinea-Bissau In review [19]	**Fever (at least 38.0°C)** 24% with misoprostol (600 micrograms sublingually) 3% with placebo Absolute numbers not reported	RR 7.09 95% CI 3.84 to 13.1	●●●	placebo

Sublingual misoprostol versus oxytocin:

We found one systematic review (search date 2007). [19] The review identified two RCTs comparing sublingual misoprostol versus oxytocin. [19] There was no meta-analysis for this particular comparison; therefore, the RCTs were reported separately. [33] [34] We also found one subsequent RCT. [18]

Postpartum haemorrhage

Compared with oxytocin Sublingual misoprostol and oxytocin seem equally effective at reducing postpartum haemorrhage (defined as blood loss of 500 mL) or severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), and at improving other measures of blood loss (volume of blood loss and haemoglobin levels) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated methylergonovine (0.2 mg im)	**Blood loss of at least 1000 mL** 1/25 (4%) with misoprostol (50 micrograms sublingually) 3/25 (12%) with oxytocin (16 mIU/minute) after cord clamping 50 women in this analysis	RR 0.33 for misoprostol *v* oxytocin 95% CI 0.04 to 2.99	⟷	Not significant
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Blood loss of at least 1000 mL** 6/50 (12%) with misoprostol (400 micrograms sublingually) 10/50 (20%) with oxytocin (20 IU iv) after delivery	RR 0.60 95% CI 0.24 to 1.53	⟷	Not significant
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated methylergonovine (0.2 mg im)	**Blood loss of at least 500 mL** 7/25 (28%) with misoprostol (50 micrograms sublingually) 8/25 (32%) with oxytocin (16 mIU/minute) after cord clamping 50 women in this analysis	RR 0.88 for misoprostol *v* oxytocin 95% CI 0.37 to 2.5	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Blood loss of at least 500 mL** 47/50 (94%) with misoprostol (400 micrograms sublingually) 46/50 (92%) with oxytocin (20 IU iv) after delivery	RR 1.02 95% CI 0.92 to 1.14	⟷	Not significant
Blood loss (volume)					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated methylergonovine (0.2 mg im)	**Mean blood loss** 389.4 mL with misoprostol (50 micrograms sublingually) 467.4 mL with oxytocin (16 mIU/minute) after cord clamping 50 women in this analysis	Mean difference –78 mL for misoprostol *v* oxytocin 95% CI –281.7 mL to +125.7 mL	⟷	Not significant
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Estimated blood loss** 819 mL with misoprostol (400 micrograms sublingually) 974 mL with oxytocin (20 IU iv) after delivery	Mean difference –155 mL 95% CI –258.9 mL to –51.6 mL	○○○	sublingual misoprostol
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Mean blood loss , third and fourth stages of labour** 96 mL with misoprostol (600 micrograms sublingually) 126 mL with misoprostol (400 micrograms sublingually) 154.7 mL with oxytocin (5 IU iv) 223 mL with methylergometrine (200 micrograms iv)	P <0.01 for sublingual misoprostol 600 micrograms *v* any other group	○○○	sublingual misoprostol 600 micrograms
Blood transfusion					
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for blood transfusion** 0/75 (0%) with misoprostol (600 micrograms sublingually) 0/75 (0%) with misoprostol (400 micrograms sublingually) 0/75 (0%) with oxytocin (5 IU iv) 3/75 (4%) with methylergometrine (200 micrograms iv)	Significance not assessed		
Postpartum haemoglobin/haematocrit level					
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Haemoglobin difference** 0.4 mL with misoprostol (400 micrograms sublingually) 0.6 mL with oxytocin (20 IU iv) after delivery	Mean difference –0.2 mL 95% CI –0.88 mL to +0.48 mL	⟷	Not significant

Need for additional medical treatment

Compared with oxytocin Sublingual misoprostol and oxytocin seem equally effective at reducing the need for additional oxytocics (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Need for additional oxytocics** 16/50 (32%) with misoprostol (400 micrograms sublingually) 18/50 (36%) with oxytocin (20 IU iv) after delivery	RR 0.89 95% CI 0.51 to 1.54	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for additional oxytocics** 0/75 (0%) with misoprostol (600 micrograms sublingually) 2/75 (3%) with misoprostol (400 micrograms sublingually) 2/75 (3%) with oxytocin (5 IU iv) 11/75 (15%) with methylergometrine (200 micrograms iv)	Significance not assessed		

No data from the following reference on this outcome. [33]

Mortality

No data from the following reference on this outcome. [33] [34] [18]

Maternal morbidity

No data from the following reference on this outcome. [33] [34] [18]

Need for additional surgical treatment

No data from the following reference on this outcome. [33] [34] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated methylergonovine (0.2 mg im)	**Vomiting** 0/25 (0%) with misoprostol (50 micrograms sublingually) 1/25 (4%) with oxytocin (16 mIU/minute) after cord clamping 50 women in this analysis	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Vomiting** 8/50 (16%) with misoprostol (400 micrograms sublingually) 6/50 (12%) with oxytocin (20 IU iv) after delivery	RR 1.33 95% CI 0.50 to 3.56	⟷	Not significant
Shivering					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated methylergonovine (0.2 mg im)	**Chills** 1/25 (4%) with misoprostol (50 micrograms sublingually) 0/25 (0%) with oxytocin (16 mIU/minute) after cord clamping 50 women in this analysis	Significance not assessed		
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Shivering** 13/50 (26%) with misoprostol (400 micrograms sublingually) 2/50 (4%) with oxytocin (20 IU iv) after delivery	RR 6.5 95% CI 1.6 to 27.3	●●●	oxytocin
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Shivering** 6/75 (8%) with misoprostol (600 micrograms sublingually) 13/75 (17%) with misoprostol (400 micrograms sublingually) 0/75 (0%) with oxytocin (5 IU iv) 0/75 (0%) with methylergometrine (200 micrograms iv)	Significance not assessed		
Fever					
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Fever** 8/50 (16%) with misoprostol (400 micrograms sublingually) 2/50 (4%) with oxytocin (20 IU iv) after delivery	RR 4.0 95% CI 0.89 to 17.91	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Pyrexia (temperature 100–101°F [approx 38.0°C]) , 1 hour after delivery** 16/75 (21%) with misoprostol (600 micrograms sublingually) 9/75 (12%) with misoprostol (400 micrograms sublingually) 0/75 (0%) with oxytocin (5 IU iv) 0/75 (0%) with methylergometrine (200 micrograms iv)	P <0.001 for either dose of misoprostol *v* other interventions	○○○	oxytocin or methylergometrine
Headache					
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Headache** 6/50 (12%) with misoprostol (400 micrograms sublingually) 8/50 (16%) with oxytocin (20 IU iv) after delivery	RR 0.75 95% CI 0.28 to 2.00	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Other adverse effects					
[34] RCT	100 women undergoing elective or emergency caesarean delivery in India In review [19]	**Metallic taste** 7/50 (14%) with misoprostol (400 micrograms sublingually) 0/50 (0%) with oxytocin (20 IU iv) after delivery	P = 0.01	○○○	oxytocin
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Increase in blood pressure** no data with oxytocin (5 IU iv) 58/75 (77%) with methylergometrine (200 micrograms iv) no data with misoprostol (600 micrograms sublingually) no data with misoprostol (400 micrograms sublingually)	Despite increase in blood pressure in women receiving methylergometrine, blood pressure remained lower than 150 mmHg systolic Significance not assessed		

Sublingual misoprostol versus carboprost:

We found no systematic reviews but found one RCT. [24]

Postpartum haemorrhage

Compared with carboprost Sublingual misoprostol and carboprost may be equally effective at reducing postpartum haemorrhage and need for blood transfusion (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Postpartum haemorrhage (blood loss of at least 500 mL)** 8/66 (12%) with misoprostol (400 micrograms sublingually) 12/67 (18%) with methylergometrine (0.2 mg iv) 13/66 (20%) with carboprost tromethamine (250 micrograms im)	P = 0.49 among all 3 groups	⟷	Not significant
Mean blood loss					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Median blood loss** 223.5 mL with misoprostol (400 micrograms sublingually) 194 mL with methylergometrine (0.2 mg iv) 227 mL with carboprost tromethamine (250 micrograms im)	P = 0.57 among all 3 groups	⟷	Not significant

Need for additional medical treatment

Compared with carboprost Sublingual misoprostol and carboprost may be equally effective at reducing the need for additional oxytocics (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Need for additional oxytocics** 9/66 (14%) with misoprostol (400 micrograms sublingually) 9/66 (13%) with carboprost tromethamine (250 micrograms im) 14/67 (21%) with methylergometrine (0.2 mg iv)	P = 0.41 among all 3 groups	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal adverse effects					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Nausea** 6/66 (9%) with misoprostol (400 micrograms sublingually) 2/67 (3%) with carboprost tromethamine (250 micrograms im) 1/67 (1%) with methylergometrine (0.2 mg iv)	P = 0.10 among all 3 groups	⟷	Not significant
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Vomiting** 8/66 (12%) with misoprostol (400 micrograms sublingually) 1/67 (1%) with carboprost tromethamine (250 micrograms im) 1/67 (1%) with methylergometrine (0.2 mg iv)	P = 0.006 for sublingual misoprostol *v* either other intervention	○○○	carboprost or methylergometrine
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Diarrhoea** 1/66 (2%) with misoprostol (400 micrograms sublingually) 7/67 (10%) with carboprost tromethamine (250 micrograms im) 0/67 (0%) with methylergometrine (0.2 mg iv)	P = 0.004 for carboprost *v* either other intervention	○○○	sublingual misoprostol or methylergometrine
Abdominal pain					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Abdominal pain** 2/66 (3%) with misoprostol (400 micrograms sublingually) 2/67 (3%) with carboprost tromethamine (250 micrograms im) 0/67 (0%) with methylergometrine (0.2 mg iv)	P = 0.47 among all 3 groups	⟷	Not significant
Shivering					
[24] RCT	200 low-risk women having vaginal deliveries in India	**Shivering** 29/66 (44%) with misoprostol (400 micrograms sublingually)	P = 0.001 for misoprostol *v* either other intervention	○○○	methylergometrine or carboprost

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial		0/67 (0%) with carboprost tromethamine (250 micrograms im) 4/67 (6%) with methylergometrine (0.2 mg iv)			
Fever					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Fever (temperature over 38.0°C)** 13/66 (20%) with misoprostol (400 micrograms sublingually) 1/67 (1%) with carboprost tromethamine (250 micrograms im) 0/67 (0%) with methylergometrine (0.2 mg iv)	P = 0.001 for misoprostol *v* either other intervention	○○○	methylergometrine or carboprost

Sublingual misoprostol versus ergometrine:

We found one systematic review (search date 2007) comparing sublingual misoprostol versus injectable uterotonics. [19] The review identified two RCTs comparing sublingual misoprostol (50–400 micrograms) versus ergometrine. [35] [33] We found one additional RCT [36] and three subsequent RCTs. [18] [24] [37]

Postpartum haemorrhage

Compared with ergometrine Sublingual misoprostol and ergometrine are equally effective at reducing postpartum haemorrhage (defined as blood loss of 500 mL) and severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), as well as other measures of blood loss including total volume of blood loss, need for transfusion, mean haemoglobin, and change in haematocrit level (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated oxytocin (16 mIU/minute) after cord clamping	**Blood loss of at least 1000 mL** 1/25 (4%) with misoprostol (50 micrograms sublingually) 3/25 (12%) with methylergonovine (0.2 mg im) 50 women in this analysis	RR 0.33 for misoprostol *v* methylergonovine 95% CI 0.04 to 2.99	⟷	Not significant
[35] RCT	120 low-risk women in India In review [19]	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 0/60 (0%) with misoprostol (400 micrograms sublingually) 0/60 (0%) with methylergometrine (200 micrograms im)			
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated oxytocin (16 mIU/minute) after cord clamping	**Blood loss of at least 500 mL** 7/25 (28%) with misoprostol (50 micrograms sublingually) 12/25 (48%) with methylergonovine (0.2 mg im) 50 women in this analysis	RR 0.58 for misoprostol *v* methylergonovine 95% CI 0.28 to 1.3	⟷	Not significant
[35] RCT	120 low-risk women in India	**Postpartum haemorrhage (blood loss of at least 500 mL)**	P = 0.50	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [19]	2/60 (3%) with misoprostol (400 micrograms sublingually) 0/60 (0%) with methylergometrine (200 micrograms im)			
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Blood loss of at least 500 mL** 1/100 (1%) with misoprostol (400 micrograms sublingually) 0/100 (0%) with methylergometrine (200 micrograms im) after delivery	P = 1.0	⟷	Not significant
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Postpartum haemorrhage (blood loss of at least 500 mL)** 8/66 (12%) with misoprostol (400 micrograms sublingually) 12/67 (18%) with methylergometrine (0.2 mg iv) 13/66 (20%) with carboprost tromethamine (250 micrograms im)	P = 0.49 among all 3 groups	⟷	Not significant
[37] RCT **3-armed trial**	300 women with term gestation and spontaneous onset of labour, all parity 5 or less, deemed to be "at low risk"	**Postpartum haemorrhage (blood loss of at least 500 mL)** with misoprostol (100 micrograms sublingually) with misoprostol (400 micrograms sublingually) with methylergometrine (1 mL iv) Absolute results not reported	No women had postpartum haemorrhage		
Blood loss (volume)					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated oxytocin (16 mIU/minute) after cord clamping	**Blood loss** 389.4 mL with misoprostol (50 micrograms sublingually) 546.8 mL with methylergonovine (0.2 mg im) 50 women in this analysis	Mean difference –157 mL for misoprostol *v* methylergonovine 95% CI –331.9 mL to +17.1 mL	⟷	Not significant
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Mean total blood loss** 137.6 mL with misoprostol (400 micrograms sublingually) 125.79 mL with methylergometrine (200 micrograms im) after delivery	P = 0.25	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Mean blood loss , third and fourth stages of labour** 154.7 mL with oxytocin (5 IU iv) 223.5 mL with methylergometrine (200 micrograms iv) 96 mL with misoprostol (600 micrograms sublingually) 126 mL with misoprostol (400 micrograms sublingually)	P <0.01 for sublingual misoprostol 600 micrograms *v* any other group	○○○	sublingual misoprostol 600 micrograms
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Mean blood loss** 223.5 mL with misoprostol (400 micrograms sublingually)	P = 0.57 among all 3 groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		194 mL with methylergometrine (0.2 mg iv) 227 mL with carboprost tromethamine (250 micrograms im)			
[37] RCT **3-armed trial**	300 women with term gestation and spontaneous onset of labour, all parity 5 or less, deemed to be "at low risk"	**Mean blood loss** 150 mL with misoprostol (100 micrograms sublingually) 150 mL with misoprostol (400 micrograms sublingually) 150 mL with methylergometrine (1 mL iv) Absolute results not reported The mean blood loss estimates in this trial are lower than would normally be expected in this population	P >0.05 The RCT did not report how many of the women randomised were followed up	⟷	Not significant
Blood transfusion					
[35] RCT	120 low-risk women in India In review [19]	**Blood transfusion** 0/60 (0%) with misoprostol (400 micrograms sublingually) 0/60 (0%) with methylergometrine (200 micrograms im)			
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for blood transfusion** 0/75 (0%) with oxytocin (5 IU iv) 3/75 (4%) with methylergometrine (200 micrograms iv) 0/75 (0%) with misoprostol (600 micrograms sublingually) 0/75 (0%) with misoprostol (400 micrograms sublingually)	Significance not assessed		
Postpartum haemoglobin/haematocrit level					
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Mean fall in haemoglobin** 0.31 g/dL with misoprostol (400 micrograms sublingually) 0.25 g/dL with methylergometrine (200 micrograms im) after delivery	P = 0.12	⟷	Not significant
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Change in haematocrit of at least 10%** 2/100 (2%) with misoprostol (400 micrograms sublingually) 1/100 (1%) with methylergometrine (200 micrograms im) after delivery	P = 1.0	⟷	Not significant

Need for additional medical treatment

Compared with ergometrine Sublingual misoprostol and ergometrine seem equally effective at reducing the need for additional medical treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[35] RCT	120 low-risk women in India In review [19]	**Need for further medical treatment** 5/60 (8%) with misoprostol (400 micrograms sublingually) 3/60 (5%) with methylergometrine (200 micrograms im)	P = 0.71	⟷	Not significant
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Use of additional oxytocics** 4/100 (4%) with misoprostol (400 micrograms sublingually) 2/100 (2%) with methylergometrine (200 micrograms im) after delivery	P = 0.68	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Need for additional oxytocics** 2/75 (3%) with oxytocin (5 IU iv) 11/75 (15%) with methylergometrine (200 micrograms iv) 0/75 (0%) with misoprostol (600 micrograms sublingually) 2/75 (3%) with misoprostol (400 micrograms sublingually)	Significance not assessed		
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Need for additional oxytocics** 9/66 (14%) with misoprostol (400 micrograms sublingually) 14/67 (21%) with methylergometrine (0.2 mg iv) 9/66 (13%) with carboprost tromethamine (250 micrograms im)	P = 0.41 among all 3 groups	⟷	Not significant
[37] RCT **3-armed trial**	300 women with term gestation and spontaneous onset of labour, all parity 5 or less, deemed to be "at low risk"	**Need for additional oxytocics** 8/100 (8%) with misoprostol (100 micrograms sublingually) 7/100 (7%) with misoprostol (400 micrograms sublingually) 5/100 (5%) with methylergometrine (1 mL iv) Absolute results not reported	P >0.05 The RCT did not report how many of the women randomised were followed up; see further information about studies for more data on this outcome	⟷	Not significant

No data from the following reference on this outcome. [33]

Need for additional surgical treatment

Compared with ergometrine Sublingual misoprostol and ergometrine seem equally effective at reducing the need for manual removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional surgical treatment					
[35] RCT	120 low-risk women in India In review [19]	**Need for manual placenta removal** 0/60 (0%) with misoprostol (400 micrograms sublingually) 1/60 (2%) with methylergometrine (200 micrograms im)	P = 1.0	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Manual placenta removal** 0/100 (0%) with misoprostol (400 micrograms sublingually) 1/100 (1%) with methylergometrine (200 micrograms im) after delivery	P = 1.0	⟷	Not significant

No data from the following reference on this outcome. [33] [37] [18] [24]

Mortality

No data from the following reference on this outcome. [33] [35] [36] [37] [18] [24]

Maternal morbidity

No data from the following reference on this outcome. [33] [35] [36] [37] [18] [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[35] RCT	120 low-risk women in India In review [19]	**Nausea** 13% with misoprostol (400 micrograms sublingually) 7% with methylergometrine (200 micrograms im) Absolute numbers not reported	RR 2.00 95% CI 0.64 to 6.2	⟷	Not significant
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Nausea** 4/100 (4%) with misoprostol (400 micrograms sublingually) 2/100 (2%) with methylergometrine (200 micrograms im) after delivery	P = 0.68	⟷	Not significant
[35] RCT	120 low-risk women in India In review [19]	**Vomiting** 7% with misoprostol (400 micrograms sublingually) 3% with methylergometrine (200 micrograms im) Absolute numbers not reported	RR 2.00 95% CI 0.38 to 10.51	⟷	Not significant
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Nausea** 6/66 (9%) with misoprostol (400 micrograms sublingually) 1/67 (1%) with methylergometrine (0.2 mg iv)	P = 0.10 among all 3 groups	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		2/67 (3%) with carboprost tromethamine (250 micrograms im)			
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Vomiting** 8/66 (12%) with misoprostol (400 micrograms sublingually) 1/67 (1%) with methylergometrine (0.2 mg iv) 1/67 (1%) with carboprost tromethamine (250 micrograms im)	P = 0.006 for sublingual misoprostol *v* either other intervention	○○○	carboprost or methylergometrine
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Diarrhoea** 1/66 (2%) with misoprostol (400 micrograms sublingually) 0/67 (0%) with methylergometrine (0.2 mg iv) 7/67 (10%) with carboprost tromethamine (250 micrograms im)	P = 0.004 for carboprost *v* either other intervention	○○○	sublingual misoprostol or methylergometrine
Abdominal pain					
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Abdominal pain** 2/66 (3%) with misoprostol (400 micrograms sublingually) 0/67 (0%) with methylergometrine (0.2 mg iv) 2/67 (3%) with carboprost tromethamine (250 micrograms im)	P = 0.47 among all 3 groups	⟷	Not significant
Shivering					
[33] RCT **3-armed trial**	75 women in Colombia In review [19] The remaining arm evaluated oxytocin (16 mIU/minute) after cord clamping	**Chills** 1/25 (4%) with misoprostol (50 micrograms sublingually) 1/25 (4%) with methylergonovine (0.2 mg im) 50 women in this analysis	Significance not assessed		
[35] RCT	120 low-risk women in India In review [19]	**Shivering** 22% with misoprostol (400 micrograms sublingually) 0% with methylergometrine (200 micrograms im) Absolute numbers not reported	P = 0.0001	○○○	methylergometrine
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Shivering** 18/100 (18%) with misoprostol (400 micrograms sublingually) 4/100 (4%) with methylergometrine (200 micrograms im) after delivery	P = 0.003	○○○	methylergometrine
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Shivering , 1 hour after delivery** 6/75 (8%) with misoprostol (600 micrograms sublingually) 13/75 (17%) with misoprostol (400 micrograms sublingually) 0/75 (0%) with oxytocin (5 IU iv)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/75 (0%) with methylergometrine (200 micrograms iv)			
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Shivering** 29/66 (44%) with misoprostol (400 micrograms sublingually) 4/67 (6%) with methylergometrine (0.2 mg iv) 0/67 (0%) with carboprost tromethamine (250 micrograms im)	P = 0.001 for misoprostol *v* either other intervention	○○○	methylergometrine or carboprost
Fever					
[35] RCT	120 low-risk women in India In review [19]	**Fever** 7% with misoprostol (400 micrograms sublingually) 0% with methylergometrine (200 micrograms im) Absolute numbers not reported	P = 0.06	⟷	Not significant
[36] RCT	200 women at low risk for postpartum haemorrhage in India	**Fever (at least 38.0°C)** 6/100 (6%) with misoprostol (400 micrograms sublingually) 1/100 (1%) with methylergometrine (200 micrograms im) after delivery	P = 0.11	⟷	Not significant
[18] RCT **4-armed trial**	300 women undergoing vaginal delivery in India	**Pyrexia (temperature 100–101°F [approx 38.0°C]) , 1 hour after delivery** 9/75 (12%) with misoprostol (600 micrograms sublingually) 16/75 (21%) with misoprostol (400 micrograms sublingually) 0/75 (0%) with oxytocin (5 IU iv) 0/75 (0%) with methylergometrine (200 micrograms iv)	P <0.001 for either dose of misoprostol *v* other interventions None of the participants were febrile at 4 hours	○○○	oxytocin or methylergometrine
[24] RCT **3-armed trial**	200 low-risk women having vaginal deliveries in India	**Fever (temperature over 38.0°C)** 13/66 (20%) with misoprostol (400 micrograms sublingually) 0/67 (0%) with methylergometrine (0.2 mg iv) 1/67 (1%) with carboprost tromethamine (250 micrograms im)	P = 0.001 for misoprostol *v* either other intervention	○○○	methylergometrine or carboprost
Headache					
[35] RCT	120 low-risk women in India In review [19]	**Headache** 7% with misoprostol (400 micrograms sublingually) 5% with methylergometrine (200 micrograms im) Absolute numbers not reported	RR 1.33 95% CI 0.31 to 5.70	⟷	Not significant
Other adverse effects					
[18] RCT	300 women undergoing vaginal delivery in India	**Increase in blood pressure** no data with oxytocin (5 IU iv)	Despite increase in blood pressure in women receiving methy-		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial		58/75 (77%) with methylergometrine (200 micrograms iv) no data with misoprostol (600 micrograms) no data with misoprostol (400 micrograms)	lergometrine, blood pressure remained lower than 150 mmHg systolic Significance not assessed		

Sublingual misoprostol versus oxytocin plus ergometrine:

We found one systematic review (search date 2007) [19] comparing sublingual misoprostol versus all injectable uterotonics, which identified one RCT. [38]

Postpartum haemorrhage

Compared with oxytocin plus ergometrine combinations We don't know whether sublingual misoprostol is more effective than oxytocin plus ergometrine at reducing blood loss (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[38] RCT	60 women in Hong Kong In review [19]	**Blood loss** 187 mL with misoprostol (600 micrograms sublingually) 183 mL with fixed combination of oxytocin plus ergometrine (1 mL)	Mean difference +4 mL 95% CI –10.73 mL to +18.73 mL	⟷	Not significant

Need for additional surgical treatment

Compared with oxytocin plus ergometrine combinations We don't know whether sublingual misoprostol is more effective than oxytocin plus ergometrine at reducing the risk of hysterectomy (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Hysterectomy					
[38] RCT	60 women in Hong Kong In review [19]	**Hysterectomy** 1 with misoprostol (600 micrograms sublingually) 0 with fixed combination of oxytocin plus ergometrine (1 mL) The woman in the misoprostol group had a 4-L haemorrhage	Significance not assessed		

Mortality

No data from the following reference on this outcome. [38]

Maternal morbidity

No data from the following reference on this outcome. [38]

Need for additional medical treatment

No data from the following reference on this outcome. [38]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Shivering and fever					
[38] RCT	60 women in Hong Kong In review [19]	**Shivering and fever** 33% with misoprostol (600 micrograms sublingually) 0% with fixed combination of oxytocin plus ergometrine (1 mL)	P = 0.001	○○○	oxytocin plus ergometrine

Further information on studies

[37] The percentages reported above on the outcome of need for additional oxytocics are taken from the table in the published article. In the text of the article, the percentages reported are 5% with misoprostol 100 micrograms, 4% with misoprostol 400 micrograms, and 3% with methylergometrine. The RCT found no significant difference across the three groups in nausea, vomiting, temperature 38.0°C or higher, shivering, headache, or dizziness (P >0.05 for all outcomes). However, increased frequencies of several of these adverse effects were observed, and statistical comparisons were limited by power and the three-group comparison.

Comment: **Clinical guide:**
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration — making it potentially ideal for low-resource settings. Unlike other modes of administration, which have not been shown to be better than placebo/no intervention, a single RCT showed sublingual misoprostol to be more effective than placebo at preventing severe postpartum haemorrhage, but with significant adverse effects. It is unclear, given the many other studies that showed no effect compared with placebo, whether this reflects something unique about the mode of administration — for instance, more rapid absorption — or a spurious result. Further studies of sublingual administration would be helpful. Given that it is, at best, equivalent to oxytocin and ergot compounds, and has a worse adverse-effect profile, oxytocin or an ergot compound is preferred when available. If misoprostol is used, current data support sublingual administration.

OPTION MISOPROSTOL (ORAL)

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Oral misoprostol seems ineffective compared with placebo when administered orally, and is associated with adverse effects including shivering and fever.

Benefits and harms

Oral misoprostol versus placebo/no intervention:

We found one systematic review (search date 2007), [19] which included a subgroup analysis comparing oral misoprostol versus placebo or no intervention (7 RCTs, 5153 women). The RCTs identified by the review used different doses of misoprostol and different controls (see further information on studies for full details). The systematic review reported significant qualitative and statistical heterogeneity for the outcome of severe postpartum haemorrhage (P value not reported); therefore, data were reported for individual RCTs. [19] We also found one further report of one of the RCTs identified by the review that assessed only adverse effects. [39]

Mortality

Compared with placebo/no intervention Oral misoprostol is no more effective than placebo or no intervention at reducing maternal mortality (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[19] Systematic review	2849 women 2 RCTs in this analysis	**Maternal death** 2/1442 (0.13%) with misoprostol 1/1407 (0.07%) with placebo	RR 1.16 95% CI 0.24 to 8.81	⟷	Not significant

Postpartum haemorrhage

Compared with placebo/no intervention We don't know whether oral misoprostol is more effective than placebo or no intervention at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL), severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), or other measures of blood loss (volume and need for transfusion) (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 16/186 (7%) with misoprostol (600 micrograms) 13/220 (6%) with no uterotonic	RR 1.46 95% CI 0.72 to 2.95	⟷	Not significant
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 2/629 (0.3%) with misoprostol (600 micrograms) 4/599 (0.6%) with no intervention (ergometrine)	RR 0.48 95% CI 0.09 to 2.59	⟷	Not significant
[19] Systematic review	1620 women with vaginal delivery in India Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 2/812 (0.2%) with misoprostol (600 micrograms) 10/808 (1.2%) with placebo	RR 0.20 95% CI 0.04 to 0.91	●●○	misoprostol
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 17/200 (9%) with misoprostol (600 micrograms) 6/200 (3%) with placebo 400 women in this analysis	RR 2.83 for misoprostol (600 micrograms) *v* placebo 95% CI 1.14 to 7.04	●●○	placebo
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 16/200 (8%) with misoprostol (400 micrograms) 6/200 (3%) with placebo 400 women in this analysis	RR 2.67 for misoprostol (400 micrograms) *v* placebo 95% CI 1.07 to 6.68	●●○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 27/300 (9%) with misoprostol (600 micrograms) 29/299 (10%) with placebo	RR 0.93 95% CI 0.56 to 1.53	⟷	Not significant
[19] Systematic review	500 women in South Africa Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 15/250 (6%) with misoprostol (400 micrograms) 23/250 (9%) with placebo	RR 0.65 95% CI 0.35 to 1.22	⟷	Not significant
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 52/186 (28%) with misoprostol (600 micrograms) 60/220 (27%) with no uterotonic	RR 1.03 95% CI 0.75 to 1.41	⟷	Not significant
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 69/629 (11%) with misoprostol (600 micrograms) 75/599 (13%) with no intervention (ergometrine)	RR 0.91 95% CI 0.67 to 1.25	⟷	Not significant
[19] Systematic review	1620 women with vaginal delivery in India Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 52/812 (6%) with misoprostol (600 micrograms) 97/808 (12%) with placebo	RR 0.53 95% CI 0.39 to 0.74	●○○	misoprostol
[19] Systematic review	65 women with vaginal delivery in Switzerland Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 2/31 (6%) with misoprostol (600 micrograms) 5/34 (15%) with placebo	RR 0.44 95% CI 0.09 to 2.10	⟷	Not significant
Blood loss (volume)					
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Blood loss** 281 mL with misoprostol (600 micrograms) 292 mL with no intervention (ergometrine)	WMD –11.00 mL 95% CI –30.75 mL to +8.75 mL	⟷	Not significant
[19] Systematic review	1620 women with vaginal delivery in India Data from 1 RCT	**Blood loss** 214.00 mL with misoprostol (600 micrograms) 262.30 mL with placebo	WMD –48.00 mL 95% CI –65.19 mL to –30.81 mL	○○○	misoprostol
[19] Systematic review	65 women with vaginal delivery in Switzerland Data from 1 RCT	**Blood loss** 345 mL with misoprostol (600 micrograms) 417 mL with placebo	Difference –72.0 mL 95% CI –122.9 mL to –21.1 mL	○○○	misoprostol
Blood transfusion					
[19] Systematic review	2619 women 3 RCTs in this analysis	**Blood transfusion** 2/1311 (0.1%) with misoprostol (600 micrograms)	RR 0.24 95% CI 0.06 to 0.94	●●○	misoprostol

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		10/1308 (0.9%) with placebo			
[19] Systematic review	900 women 2 RCTs in this analysis	**Blood transfusion** 1/450 (0.2%) with misoprostol (400 micrograms) 2/450 (0.4%) with placebo	RR 0.60 95% CI 0.08 to 4.52	⟷	Not significant

Need for additional medical treatment

Compared with placebo/no intervention Oral misoprostol is no more effective than placebo or no intervention at reducing the need for additional medical treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	1620 women with vaginal delivery in India Data from 1 RCT	**Additional uterotonics** 3/812 (0.3%) with oral misoprostol (600 micrograms) 6/808 (0.7%) with placebo	RR 0.50 95% CI 0.12 to 1.98	⟷	Not significant
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Additional uterotonics** 32/200 (16%) with oral misoprostol (600 micrograms) 23/200 (12%) with placebo 400 women in this analysis	RR 1.39 for misoprostol (600 micrograms) *v* placebo 95% CI 0.85 to 2.29	⟷	Not significant
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Additional uterotonics** 28/200 (14%) with oral misoprostol (400 micrograms) 23/200 (12%) with placebo 400 women in this analysis	RR 1.22 for misoprostol (400 micrograms) *v* placebo 95% CI 0.73 to 2.04	⟷	Not significant
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Additional uterotonics** 42/300 (14%) with oral misoprostol (600 micrograms) 54/300 (18%) with placebo	RR 0.78 95% CI 0.54 to 1.13	⟷	Not significant
[19] Systematic review	500 women in South Africa Data from 1 RCT	**Additional uterotonics** 21/250 (8%) with oral misoprostol (400 micrograms) 33/250 (13%) with placebo	RR 0.64 95% CI 0.38 to 1.07	⟷	Not significant
[19] Systematic review	65 women with vaginal delivery in Switzerland Data from 1 RCT	**Additional uterotonics** 5/31 (16%) with oral misoprostol (600 micrograms) 13/34 (38%) with placebo	RR 0.42 95% CI 0.17 to 1.05	⟷	Not significant

Need for additional surgical treatment

Compared with placebo/no intervention Oral misoprostol is no more effective than placebo or no intervention at reducing the need for manual removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[19] Systematic review	1000 women 2 RCTs in this analysis	**Manual removal of placenta** 4/500 (0.8%) with misoprostol (600 micrograms) 3/500 (0.6%) with placebo	RR 1.33 95% CI 0.30 to 5.93	⟷	Not significant
[19] Systematic review	900 women 2 RCTs in this analysis	**Manual removal of placenta** 1/450 (0.2%) with misoprostol (400 micrograms) 3/450 (0.6%) with placebo	RR 0.43 95% CI 0.06 to 2.89	⟷	Not significant

Maternal morbidity

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Nausea** 6/630 (1%) with oral misoprostol (600 micrograms) 14/599 (2%) with no treatment (ergometrine)	RR 0.41 95% CI 0.16 to 1.05	⟷	Not significant
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (400 micrograms)	**Nausea** 1/199 (0.5%) with oral misoprostol (600 micrograms) 0/199 (0%) with placebo 400 women in this analysis	RR 3.00 for oral misoprostol (600 micrograms) *v* placebo 95% CI 0.12 to 73.20	⟷	Not significant
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (600 micrograms)	**Nausea** 1/199 (0.5%) with oral misoprostol (400 micrograms) 0/199 (0%) with placebo 400 women in this analysis	RR 3.00 for oral misoprostol (400 micrograms) *v* placebo 95% CI 0.12 to 73.20	⟷	Not significant
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Nausea** 5/300 (2%) with oral misoprostol (600 micrograms) 1/300 (0.3%) with placebo	RR 5.00 95% CI 0.59 to 42.54	⟷	Not significant
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Vomiting** 7/186 (4.0%) with oral misoprostol (600 micrograms) 1/220 (0.4%) with placebo	RR 8.28 95% CI 1.03 to 66.68	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Vomiting** 18/630 (3%) with oral misoprostol (600 micrograms) 34/599 (6%) with no intervention (ergometrine)	RR 0.50 95% CI 0.29 to 0.88	●○○	misoprostol
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (400 micrograms)	**Vomiting** 1/199 (0.5%) with oral misoprostol (600 micrograms) 1/199 (0.5%) with placebo 400 women in this analysis	RR 1.00 for oral misoprostol (600 micrograms) *v* placebo 95% CI 0.06 to 15.88	⟷	Not significant
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (600 micrograms)	**Vomiting** 1/199 (0.5%) with oral misoprostol (400 micrograms) 1/199 (0.5%) with placebo 400 women in this analysis	RR 1.00 for oral misoprostol (400 micrograms) *v* placebo 95% CI 0.06 to 15.88	⟷	Not significant
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Vomiting** 4/300 (1%) with oral misoprostol (600 micrograms) 2/300 (0.6%) with placebo	RR 2.00 95% CI 0.37 to 10.84	⟷	Not significant
[19] Systematic review	2227 women 3 RCTs in this analysis	**Diarrhoea** 7/1129 (0.6%) with misoprostol 7/1098 (0.6%) with placebo	RR 0.96 95% CI 0.34 to 2.72	⟷	Not significant
Abdominal pain					
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (400 micrograms)	**Abdominal pain** 12/199 (6%) with oral misoprostol (600 micrograms) 2/199 (1%) with placebo 400 women in this analysis	RR 6.00 for oral misoprostol (600 micrograms) *v* placebo 95% CI 1.36 to 26.46	●●●	placebo
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (600 micrograms)	**Abdominal pain** 8/199 (4%) with oral misoprostol (400 micrograms) 2/199 (1%) with placebo 400 women in this analysis	RR 4.00 for oral misoprostol (400 micrograms) *v* placebo 95% CI 0.86 to 18.60	⟷	Not significant
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Abdominal pain** 47/300 (16%) with oral misoprostol (600 micrograms) 31/300 (10%) with placebo	RR 1.52 95% CI 0.99 to 2.32	⟷	Not significant
[19] Systematic review	500 women in South Africa Data from 1 RCT	**Abdominal pain** 2/250 (1%) with oral misoprostol (400 micrograms) 7/250 (3%) with placebo	RR 0.29 95% CI 0.06 to 1.36	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Shivering					
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Shivering** 5/186 (3%) with oral misoprostol (600 micrograms) 0/220 (0%) with placebo	RR 13.00 95% CI 0.72 to 233.66	⟷	Not significant
[19] Systematic review	1229 women with vaginal delivery in Gambia Data from 1 RCT	**Shivering** 202/630 (32%) with oral misoprostol (600 micrograms) 70/599 (12%) with no intervention (ergometrine)	RR 2.74 95% CI 2.14 to 3.52	●●○	no intervention (ergometrine)
[19] Systematic review	1620 women with vaginal delivery in India Data from 1 RCT	**Shivering , 2 hours** 424/812 (52%) with oral misoprostol (600 micrograms) 140/808 (17%) with placebo	RR 3.01 95% CI 2.56 to 3.55	●●○	placebo
[39] RCT	1620 women with vaginal delivery in India In review [19] Data from 1 RCT	**Shivering , 24 hours** 37/812 (5%) with oral misoprostol (600 micrograms) 11/808 (1%) with placebo	P <0.001	○○○	placebo
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (400 micrograms)	**Shivering** 81/199 (41%) with oral misoprostol (600 micrograms) 30/199 (15%) with placebo 400 women in this analysis	RR 2.70 for oral misoprostol (600 micrograms) *v* placebo 95% CI 1.87 to 3.91	●●○	placebo
[19] Systematic review **3-armed trial**	600 women in South Africa Data from 1 RCT Remaining arm evaluated oral misoprostol (600 micrograms)	**Shivering** 65/199 (32%) with oral misoprostol (400 micrograms) 30/199 (15%) with placebo 400 women in this analysis	RR 2.17 for oral misoprostol (400 micrograms) *v* placebo 95% CI 1.47 to 3.19	●●○	placebo
[19] Systematic review	600 women in South Africa Data from 1 RCT	**Shivering** 133/300 (44%) with oral misoprostol (600 micrograms) 33/300 (11%) with placebo	RR 4.03 95% CI 2.85 to 5.70	●●○	placebo
[19] Systematic review	500 women in South Africa Data from 1 RCT	**Shivering** 48/250 (19%) with oral misoprostol (400 micrograms) 13/250 (5%) with placebo	RR 3.69 95% CI 2.05 to 6.64	●●○	placebo
[19] Systematic review	65 women with vaginal delivery in Switzerland Data from 1 RCT	**Shivering** 7/31 (23%) with oral misoprostol (600 micrograms) 1/34 (3%) with placebo	RR 7.68 95% CI 1.00 to 58.92	●●●	placebo
Fever					
[19] Systematic review	3424 women Data from 1 RCT	**Fever (at least 38°C)** 207/1697 (12%) with misoprostol 32/1727 (2%) with placebo	RR 6.40 95% CI 4.47 to 9.18	●●●	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[39] RCT	1620 women with vaginal delivery in India In review [19] Data from 1 RCT	**Fever , 2 hours** 34/812 (4%) with oral misoprostol (600 micrograms) 9/808 (1%) with placebo	P <0.001	○○○	placebo
[39] RCT	1620 women with vaginal delivery in India In review [19] Data from 1 RCT	**Fever , 24 hours** 11/812 (1.4%) with oral misoprostol (600 micrograms) 30/808 (0.4%) with placebo	P <0.03	○○○	placebo
Headache					
[19] Systematic review	998 women 2 RCTs in this analysis	**Headache** 5/499 (1%) with misoprostol (600 micrograms) 2/499 (0.4%) with placebo	RR 2.20 95% CI 0.50 to 9.77	⟷	Not significant
[19] Systematic review	398 women Data from 1 RCT	**Headache** 2/199 (1%) with misoprostol (400 micrograms) 0/199 (0%) with placebo	RR 5.00 95% CI 0.24 to 103.49	⟷	Not significant
Other adverse effects					
[19] Systematic review	500 women Data from 1 RCT	**Any adverse effect** 54/250 (22%) with misoprostol 26/250 (10%) with placebo	RR 2.08 95% CI 1.35 to 3.20	●●○	placebo

Oral misoprostol versus ergot compounds:

We found one systematic review (search date 2007), [19] which identified three RCTs comparing oral misoprostol versus an ergot compound included in this review (ergometrine/methergine). [19] We also found one subsequent RCT. [40]

Postpartum haemorrhage

Compared with ergot compounds Oral misoprostol and ergot compounds are equally effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) or severe postpartum haemorrhage (defined as blood loss of at least 1000 mL) and at reducing the need for transfusion (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 1/100 (1%) with oral misoprostol (600 micrograms) 0/100 (0%) with methylergometrine (200 micrograms)	RR 3.00 95% CI 0.12 to 72.77	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 1/730 (0.1%) with oral misoprostol (400 micrograms)	RR 0.18 for oral misoprostol *v* ergometrine 95% CI 0.02 to 1.38	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		12/1293 (0.8%) with ergometrine (0.2 mg iv)			
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 8/96 (8%) with oral misoprostol (600 micrograms) 4/93 (4%) with methylergometrine (200 micrograms)	RR 1.94 95% CI 0.60 to 6.22	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 8/100 (8%) with oral misoprostol (600 micrograms) immediately after delivery 6/100 (6%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 1.33 95% CI 0.48 to 3.70	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Postpartum haemorrhage (blood loss of at least 500 mL)** 19/730 (3%) with oral misoprostol (400 micrograms) 13/617 (2%) with ergometrine (0.2 mg iv)	RR 1.24 for oral misoprostol *v* ergometrine 95% CI 0.62 to 2.48	⟷	Not significant
[40] RCT	864 singleton low-risk pregnant women	**Postpartum haemorrhage (blood loss >500 mL)** 6/432 (1%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 42/432 (10%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.0001 This result should be interpreted in the context of its setting; the authors of the trial reported that "drugs such as methylergometrine used in this study might have lost their potency due to poor storage conditions"	○○○	oral misoprostol
Blood loss (volume)					
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Mean blood loss** 192.5 mL with oral misoprostol (400 micrograms) 183 mL with ergometrine (0.2 mg iv)	WMD +9.50 mL for oral misoprostol *v* ergometrine 95% CI –4.48 mL to +23.48 mL	⟷	Not significant
[40] RCT	864 singleton low-risk pregnant women	**Total estimated blood loss** 191.6 mL with oral misoprostol (400 micrograms) at delivery of anterior shoulder 246 mL with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.0001 This result should be interpreted in the context of its setting; the authors of the trial reported that "drugs such as methylergometrine used in this study might have lost their potency due to poor storage conditions"	○○○	oral misoprostol
Blood transfusion					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Blood transfusion** 1/100 (1%) with oral misoprostol (600 micrograms) 1/100 (1%) with methylergometrine (200 micrograms)	RR 1.00 95% CI 0.06 to 15.77	⟷	Not significant
[19] Systematic review	2023 women in India Data from 1 RCT	**Blood transfusion** 1/730 (0.1%) with oral misoprostol (400 micrograms)	RR 0.42 for oral misoprostol *v* ergometrine 95% CI 0.04 to 4.65	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	Remaining arm evaluated oxytocin im (10 IU)	2/617 (0.3%) with ergometrine (0.2 mg iv)			

Need for additional medical treatment

Compared with ergot compounds Oral misoprostol and ergot compounds are equally effective at reducing the need for additional uterotonics (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Need for additional medical treatment					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Additional uterotonics** 12/94 (13%) with oral misoprostol (600 micrograms) 4/91 (4%) with methylergometrine (200 micrograms)	RR 2.90 95% CI 0.97 to 8.67	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Additional uterotonics** 10/100 (10%) with oral misoprostol (600 micrograms) immediately after delivery 7/100 (7%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 1.43 95% CI 0.57 to 3.60	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Additional uterotonics** 63/730 (9%) with oral misoprostol (400 micrograms) 38/617 (6%) with ergometrine (0.2 mg iv)	RR 1.40 for oral misoprostol *v* ergometrine 95% CI 0.95 to 2.07	⟷	Not significant
[40] RCT	864 singleton low-risk pregnant women	**Need for additional oxytocics** 33/432 (8%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 80/432 (19%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.0001 This result should be interpreted in the context of its setting; the authors of the trial reported that "drugs such as methylergometrine used in this study might have lost their potency due to poor storage conditions"	○○○	oral misoprostol

Need for additional surgical treatment

Compared with ergot compounds Oral misoprostol and ergot compounds are equally effective at reducing the need for manual removal of the placenta (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of the placenta					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Manual placenta removal** 4/100 (4%) with oral misoprostol (600 micrograms) 3/100 (3%) with methylergometrine (200 micrograms)	RR 1.33 95% CI 0.31 to 5. 81	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Manual placenta removal** 0/100 (0%) with oral misoprostol (600 micrograms) immediately after delivery			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/100 (0%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder			
[40] RCT	864 singleton low-risk pregnant women	**Manual removal of the placenta** 23/432 (5%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 17/432 (4%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P = 0.42 This result should be interpreted in the context of its setting; the authors of the trial reported that "drugs such as methylergometrine used in this study might have lost their potency due to poor storage conditions"	⟷	Not significant

Mortality

No data from the following reference on this outcome. [19] [40]

Maternal morbidity

No data from the following reference on this outcome. [19] [40]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Nausea** 20/87 (23%) with oral misoprostol (600 micrograms) 30/94 (32%) with methylergometrine (200 micrograms)	RR 0.72 95% CI 0.44 to 1.17	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Nausea** 5/730 (1%) with oral misoprostol (400 micrograms) 11/617 (2%) with ergometrine (0.2 mg iv)	RR 0.38 for oral misoprostol *v* ergometrine 95% CI 0.13 to 1.10	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Nausea** 20/100 (20%) with oral misoprostol (600 micrograms) immediately after delivery 30/100 (30%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 0.67 95% CI 0.41 to 1.09	⟷	Not significant
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Vomiting** 13/87 (15%) with oral misoprostol (600 micrograms) 18/94 (19%) with methylergometrine (200 micrograms)	RR 0.78 95% CI 0.41 to 1.50	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Vomiting** 6/730 (0.8%) with oral misoprostol (400 micrograms) 2/617 (0.3%) with ergometrine (0.2 mg iv)	RR 2.54 95% CI 0.51 to 12.52	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Vomiting** 19/100 (19%) with oral misoprostol (600 micrograms) immediately after delivery 30/100 (30%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 0.63 95% CI 0.38 to 1.05	⟷	Not significant
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Diarrhoea** 3/100 (3%) with oral misoprostol (600 micrograms) immediately after delivery 3/100 (3%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 1.00 95% CI 0.21 to 4.84	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Diarrhoea** 1/730 (0.1%) with oral misoprostol (400 micrograms) 0/617 (0%) with ergometrine (0.2 mg iv)	RR 2.54 for oral misoprostol *v* ergometrine 95% CI 0.10 to 62.15	⟷	Not significant
[40] RCT	864 singleton low-risk pregnant women	**Vomiting** 1/432 (0.23%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 12/432 (3%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P = 0.02	○○○	oral misoprostol
[40] RCT	864 singleton low-risk pregnant women	**Nausea** 10/432 (2%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 16/432 (4%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.05	○○○	oral misoprostol
Shivering					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Shivering** 66/86 (77%) with oral misoprostol (600 micrograms) 38/94 (40%) with methylergometrine (200 micrograms)	RR 1.90 95% CI 1.45 to 2.49	●○○	methylergometrine
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Shivering** 31/100 (31%) with oral misoprostol (600 micrograms) immediately after delivery 10/100 (10%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 3.10 95% CI 1.61 to 5.98	●●○	methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Severe shivering** 2/730 (0.3%) with oral misoprostol (400 micrograms) 0/617 (0%) with ergometrine (0.2 mg iv)	RR 4.23 for oral misoprostol *v* ergometrine 95% CI 0.20 to 87.88	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women in India Data from 1 RCT Remaining arm evaluated oxytocin im (10 IU)	**Shivering** 68/730 (9%) with oral misoprostol (400 micrograms) 14/617 (2%) with ergometrine (0.2 mg iv)	RR 4.11 for oral misoprostol *v* ergometrine 95% CI 2.33 to 7.22	●●○	ergometrine
Fever					
[19] Systematic review	213 women with vaginal delivery in Belgium Data from 1 RCT	**Fever (at least 38°C)** 34/100 (34%) with oral misoprostol (600 micrograms) 3/100 (3%) with methylergometrine (200 micrograms)	RR 11.33 95% CI 3.60 to 35.70	●●●	methylergometrine
[19] Systematic review	200 women with singleton deliveries in India Data from 1 RCT	**Fever (at least 38°C)** 29/100 (29%) with oral misoprostol (600 micrograms) immediately after delivery 7/100 (7%) with methylergometrine (0.2 mg iv) at delivery of anterior shoulder	RR 4.14 95% CI 1.90 to 9.01	●●○	methylergometrine
[40] RCT	864 singleton low-risk pregnant women	**Fever >38°C** 31/432 (7%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 7/432 (2%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.005	○○○	methylergometrine
Headache					
[40] RCT	864 singleton low-risk pregnant women	**Headache** 1/432 (0.2%) with oral misoprostol (400 micrograms) at delivery of anterior shoulder 54/432 (13%) with methylergometrine (500 micrograms iv) at delivery of anterior shoulder	P <0.05	○○○	oral misoprostol

No data from the following reference on this outcome. [40]

Oral misoprostol versus oxytocin:

We found one systematic review (search date 2007; 11 RCTs in women having vaginal deliveries and 1 RCT in women having caesarean delivery) comparing oral misoprostol versus oxytocin. [19] We also found one additional RCT comparing oral misoprostol versus oxytocin that included women with caesarean delivery. [41]

Mortality

Compared with oxytocin Oral misoprostol and oxytocin may be equally effective at reducing mortality (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Mortality					
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Maternal death** 2/9264 (0.01%) with oral misoprostol (600 micrograms) 2/9266 (0.02%) with oxytocin (10 IU iv/im)	RR 1.00 95% CI 0.14 to 7.10	⟷	Not significant
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Maternal death** 0% with oral misoprostol (400 micrograms) 0% with oxytocin (5 IU im) Absolute numbers not reported			
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Maternal death** 0% with oral misoprostol (800 micrograms) 0% with oxytocin (10 IU im) Absolute numbers not reported			
[19] Systematic review **3-armed trial**	597 women with vaginal delivery (multicentre, WHO) Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Maternal death** 0% with oral misoprostol (400 micrograms) 0% with oxytocin (10 IU iv)			
[19] Systematic review **3-armed trial**	597 women with vaginal delivery (multicentre, WHO) Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Maternal death** 0% with oral misoprostol (600 micrograms) 0% with oxytocin (10 IU iv)			

Postpartum haemorrhage

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) and severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), and at reducing the need for transfusions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 13/424 (3%) with oral misoprostol (400 micrograms) 7/439 (2%) with oxytocin (10 IU im)	RR 1.92 95% CI 0.77 to 4.77	⟷	Not significant
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 14/311 (5%) with oral misoprostol (400 micrograms)	RR 2.00 95% CI 0.82 to 4.89	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		7/311 (2%) with oxytocin (5 IU im)			
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 16/186 (9%) with oral misoprostol (600 micrograms) 12/189 (6%) with oxytocin (2.5 IU iv)	RR 1.41 95% CI 0.68 to 2.89	⟷	Not significant
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 0/202 (0%) with oral misoprostol (400 micrograms) 0/196 (0%) with oxytocin (10 IU iv)			
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 0/225 (0%) with oral misoprostol (800 micrograms) 0/225 (0%) with oxytocin (10 IU im)	Significance not assessed		
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 1/730 (0.1%) with oral misoprostol (400 micrograms) 10/1293 (8%) with oxytocin (10 IU iv)	RR 0.18 for oral misoprostol *v* oxytocin 95% CI 0.02 to 1.38	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 0% with oral misoprostol (600 micrograms) 0% with oxytocin (10 IU im)	Significance not assessed		
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 14/388 (4%) with oral misoprostol (400 micrograms) 15/384 (4%) with oxytocin (10 IU iv)	RR 0.92 95% CI 0.45 to 1.89	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery (WHO) Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 14/198 (7%) with oral misoprostol (400 micrograms) 13/200 (7%) with oxytocin (10 IU iv)	RR 1.09 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.52 to 2.25	⟷	Not significant
[19] Systematic review	597 women with vaginal delivery (WHO) Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 8/199 (4%) with oral misoprostol (600 micrograms)	RR 0.62 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.26 to 1.46	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	Remaining arm evaluated misoprostol (400 micrograms)	13/200 (7%) with oxytocin (10 IU iv)			
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 366/9214 (4%) with oral misoprostol (600 micrograms) 263/9228 (3%) with oxytocin (10 IU iv/im)	RR 1.39 95% CI 1.19 to 1.63	●○○	oxytocin
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 9/243 (4%) with oral misoprostol (400 micrograms) 5/256 (2%) with oxytocin (10 IU im)	Significance not assessed		
[19] Systematic review	40 women with elective or emergency caesarean (UK) Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 3/20 (15%) with oral misoprostol (500 micrograms) 3/20 (15%) with oxytocin (10 IU iv)	RR 1.00 95% CI 0.23 to 4.37	⟷	Not significant
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 63/424 (15%) with oral misoprostol (400 micrograms) 24/439 (6%) with oxytocin (10 IU im)	RR 2.72 95% CI 1.73 to 4.27	●●○	oxytocin
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 52/186 (30%) with oral misoprostol (600 micrograms) 29/196 (6%) with oxytocin (2.5 IU iv)	RR 1.89 95% CI 1.26 to 2.84	●○○	oxytocin
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 0/202 (0%) with oral misoprostol (400 micrograms) 2/196 (1%) with oxytocin (10 IU iv)	RR 0.19 95% CI 0.01 to 4.02	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 0/225 (0%) with oral misoprostol (800 micrograms) 5/225 (2%) with oxytocin (10 IU im)	Significance not assessed		
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Postpartum haemorrhage (blood loss of at least 500 mL)** 19/170 (3%) with oral misoprostol (400 micrograms) 13/617 (2%) with oxytocin (10 IU iv)	RR 1.24 for oral misoprostol *v* oxytocin 95% CI 0.62 to 2.48	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 8/100 (8%) with oral misoprostol (600 micrograms) 6/100 (6%) with oxytocin (10 IU im)	RR 1.33 95% CI 0.48 to 3.70	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 35/388 (9%) with oral misoprostol (400 micrograms) 28/384 (7%) with oxytocin (10 IU iv)	RR 1.24 95% CI 0.77 to 1.99	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery (WHO) Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Postpartum haemorrhage (blood loss of at least 500 mL)** 51/198 (26%) with oral misoprostol (400 micrograms) 52/200 (26%) with oxytocin (10 IU iv)	RR 0.99 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.71 to 1.38	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery (WHO) Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Postpartum haemorrhage (blood loss of at least 500 mL)** 45/199 (23%) with oral misoprostol (600 micrograms) 52/200 (26%) with oxytocin (10 IU iv)	RR 0.87 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.61 to 1.23	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 1793/9213 (20%) with oral misoprostol (600 micrograms) 1248/9227 (14%) with oxytocin (10 IU iv/im)	RR 1.44 95% CI 1.35 to 1.54	●○○	oxytocin
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 36/243 (15%) with oral misoprostol (400 micrograms) 34/256 (13%) with oxytocin (10 IU im)	RR 1.15 95% CI 0.74 to 1.76	⟷	Not significant
[19] Systematic review	40 women with elective or emergency caesarean (UK) Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 17/20 (85%) with oral misoprostol (500 micrograms) 17/20 (85%) with oxytocin (10 IU iv)	RR 1.00 95% CI 0.77 to 1.30	⟷	Not significant
Blood loss (volume)					
[41] RCT	56 women with caesarean section in Switzerland Data from 1 RCT	**Calculated blood loss** 1083 mL with oral misoprostol (800 micrograms) 970 mL with oxytocin (20 IU) All women received an initial bolus of oxytocin 5 IU	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood transfusion					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Blood transfusion** 5/424 (1%) with oral misoprostol (400 micrograms) 5/439 (1%) with oxytocin (10 IU im)	RR 1.04 95% CI 0.30 to 3.55	⟷	Not significant
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Blood transfusion** 0/136 (0%) with oral misoprostol (400 micrograms) 1/138 (0.7%) with oxytocin (10 IU iv)	RR 0.34 95% CI 0.01 to 8.23	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Blood transfusion** 1/222 (0.5%) with oral misoprostol (800 micrograms) 2/221 (0.9%) with oxytocin (10 IU im)	RR 0.58 95% CI 0.05 to 5.45	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Blood transfusion** 1/730 (0.1%) with oral misoprostol (400 micrograms) 2/617 (0.3%) with oxytocin (10 IU iv)	RR 0.42 for oral misoprostol *v* oxytocin 95% CI 0.04 to 4.65	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Blood transfusion** 0% with oral misoprostol (600 micrograms) 0% with oxytocin (10 IU im)			
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Blood transfusion** 14/388 (4%) with oral misoprostol (400 micrograms) 13/384 (3%) with oxytocin (10 IU iv)	RR 1.07 95% CI 0.51 to 2.24	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Blood transfusion** 0% with oral misoprostol (400 micrograms) 0% with oxytocin (10 IU iv)			
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Blood transfusion** 0% with oral misoprostol (600 micrograms) 0% with oxytocin (10 IU iv)			
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Blood transfusion** 72/9221 (0.8%) with oral misoprostol (600 micrograms) 97/9226 (1%) with oxytocin (10 IU iv/im)	RR 0.74 95% CI 0.55 to 1.02	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Blood transfusion** 2/243 (0.8%) with oral misoprostol (400 micrograms) 1/256 (0.4%) with oxytocin (10 IU im)	RR 2.11 95% CI 0.19 to 23.09	⟷	Not significant
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Blood transfusion** 0/311 (0%) with oral misoprostol (400 micrograms) 0/311 (0%) with oxytocin (5 IU im)	Significance not assessed		

Need for additional medical treatment

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing the need for additional medical treatment (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Additional uterotonics** 95/424 (22%) with oral misoprostol (400 micrograms) 34/439 (8%) with oxytocin (10 IU im)	RR 2.89 95% CI 2.00 to 4.18	●●○	oxytocin
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Additional uterotonics** 159/311 (51%) with oral misoprostol (400 micrograms) 126/311 (40%) with oxytocin (5 IU im)	RR 1.26 95% CI 1.06 to 1.50	●○○	oxytocin
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Additional uterotonics** 6/168 (4%) with oral misoprostol (400 micrograms) 8/172 (5%) with oxytocin (10 IU iv)	RR 0.77 95% CI 0.27 to 2.17	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Additional uterotonics** 16/225 (7%) with oral misoprostol (800 micrograms) 21/225 (9%) with oxytocin (10 IU im)	RR 0.76 95% CI 0.41 to 1.42	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Additional uterotonics** 63/730 (9%) with oral misoprostol (400 micrograms) 38/617 (6%) with oxytocin (10 IU iv)	RR 1.40 for oral misoprostol *v* oxytocin 95% CI 0.95 to 2.07	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Additional uterotonics** 31/247 (13%) with oral misoprostol (600 micrograms) 27/249 (11%) with oxytocin (10 IU im)	RR 1.16 95% CI 0.71 to 1.88	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Additional uterotonics** 23/198 (12%) with oral misoprostol (400 micrograms) 28/200 (14%) with oxytocin (10 IU iv)	RR 0.83 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.50 to 1.39	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Additional uterotonics** 18/199 (9%) with oral misoprostol (600 micrograms) 28/200 (14%) with oxytocin (10 IU iv)	RR 0.45 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.37 to 1.13	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Additional uterotonics** 1398/9225 (15%) with oral misoprostol (600 micrograms) 1002/9228 (11%) with oxytocin (10 IU iv/im)	RR 1.40 95% CI 1.29 to 1.51	●○○	oxytocin
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Additional uterotonics** 13/243 (5%) with oral misoprostol (400 micrograms) 7/256 (3%) with oxytocin (10 IU im)	RR 1.96 95% CI 0.79 to 4.82	⟷	Not significant
[19] Systematic review	40 women with elective or emergency caesarean (UK) Data from 1 RCT	**Additional uterotonics** 6/20 (30%) with oral misoprostol (500 micrograms) 1/20 (5%) with oxytocin (10 IU iv)	RR 6.00 95% CI 0.79 to 45.42	⟷	Not significant

Need for additional surgical treatment

Compared with oxytocin Oral misoprostol and oxytocin seem equally effective at reducing the need for manual removal of the placenta (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of placenta					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Manual removal of placenta** 0/424 (0%) with oral misoprostol (400 micrograms) 0/439 (0%) with oxytocin (10 IU im)			
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Manual removal of placenta** 25/311 (8%) with oral misoprostol (400 micrograms) 25/311 (8%) with oxytocin (5 IU im)	RR 1.00 95% CI 0.59 to 1.70	⟷	Not significant
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Manual removal of placenta** 1/182 (0.5%) with oral misoprostol (400 micrograms) 1/187 (0.5%) with oxytocin (10 IU iv)	RR 1.03 95% CI 0.06 to 16.30	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Manual removal of placenta** 0/225 (0%) with oral misoprostol (800 micrograms) 0/225 (0%) with oxytocin (10 IU im)			
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Manual removal of placenta** 4/247 (2%) with oral misoprostol (600 micrograms) 2/249 (1%) with oxytocin (10 IU im)	RR 2.02 95% CI 0.37 to 10.91	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Manual removal of placenta** 4/198 (2%) with oral misoprostol (400 micrograms) 8/200 (4%) with oxytocin (10 IU iv)	RR 0.51 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.15 to 1.65	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Manual removal of placenta** 3/199 (2%) with oral misoprostol (600 micrograms) 8/200 (4%) with oxytocin (10 IU iv)	RR 0.38 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.10 to 1.40	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Manual removal of placenta** 219/9225 (2%) with oral misoprostol (600 micrograms) 215/9232 (2%) with oxytocin (10 IU iv/im)	RR 1.02 95% CI 0.85 to 1.23	⟷	Not significant
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Manual removal of placenta** 3/243 (1.2%) with oral misoprostol (400 micrograms) 2/256 (0.8%) with oxytocin (10 IU im)	RR 1.58 95% CI 0.27 to 9.38	⟷	Not significant

Maternal morbidity

No data from the following reference on this outcome. [41] [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Nausea** 7/243 (3%) with oral misoprostol (400 micrograms) 5/256 (2%) with oxytocin (10 IU im)	RR 1.47 95% CI 0.47 to 4.58	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Nausea** 5/152 (3%) with oral misoprostol (400 micrograms) 6/159 (4%) with oxytocin (10 IU iv)	RR 0.87 95% CI 0.27 to 2.80	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Nausea** 2/223 (1%) with oral misoprostol (800 micrograms) 4/222 (2%) with oxytocin (10 IU im)	RR 0.50 95% CI 0.09 to 2.69	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Nausea** 5/730 (1%) with oral misoprostol (400 micrograms) 11/617 (2%) with oxytocin (10 IU iv)	RR 0.38 95% CI 0.13 to 1.10	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Nausea** 8/247 (3%) with oral misoprostol (600 micrograms) 10/249 (4%) with oxytocin (10 IU im)	RR 0.81 95% CI 0.32 to 2.01	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Nausea** 77/9227 (0.8%) with oral misoprostol (600 micrograms) 34/9228 (0.4%) with oxytocin (10 IU im/iv)	RR 2.27 95% CI 1.52 to 3.39	●●○	oxytocin
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Nausea** 0/198 (0%) with oral misoprostol (400 micrograms) 1/200 (0.5%) with oxytocin (10 IU iv)	RR 0.34 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.01 to 8.22	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Nausea** 1/199 (0.5%) with oral misoprostol (600 micrograms) 1/200 (0.5%) with oxytocin (10 IU iv)	RR 1.01 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.06 to 15.96	⟷	Not significant
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Vomiting** 8/424 (2%) with oral misoprostol (400 micrograms) 15/439 (4%) with oxytocin (10 IU im)	RR 0.55 95% CI 0.24 to 1.29	⟷	Not significant
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Vomiting** 7/186 (4%) with oral misoprostol (600 micrograms) 1/196 (0.3%) with oxytocin (2.5 IU iv)	RR 7.38 95% CI 0.92 to 59.38	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Vomiting** 5/164 (3%) with oral misoprostol (400 micrograms) 4/177 (2%) with oxytocin (10 IU iv)	RR 1.35 95% 0.37 to 4.94	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Vomiting** 1/221 (0.5%) with oral misoprostol (800 micrograms) 4/224 (2%) with oxytocin (10 IU im)	RR 0.25 95% CI 0.03 to 2.25	⟷	Not significant
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Vomiting** 6/730 (0.8%) with oral misoprostol (400 micrograms) 2/617 (0.3%) with oxytocin (10 IU iv)	RR 2.54 for oral misoprostol *v* oxytocin 95% CI 0.51 to 12.52	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Vomiting** 12/247 (5%) with oral misoprostol (600 micrograms) 9/249 (4%) with oxytocin (10 IU im)	RR 1.34 95% CI 0.58 to 3.13	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Vomiting** 4/388 (1%) with oral misoprostol (400 micrograms) 3/384 (0.7%) with oxytocin (10 IU iv)	RR 1.32 95% CI 0.30 to 5.86	⟷	Not significant
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Vomiting** 2/243 (1%) with oral misoprostol (400 micrograms) 1/256 (0.4%) with oxytocin (10 IU im)	RR 3.16 95% CI 0.33 to 30.18	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Vomiting** 66/9227 (0.7%) with oral misoprostol (600 micrograms) 25/9232 (0.3%) with oxytocin (10 IU im/iv)	RR 2.6 95% CI 1.67 to 4.18	●●○	oxytocin
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Vomiting** 0/198 (0%) with oral misoprostol (400 micrograms) 1/200 (0.5%) with oxytocin (10 IU iv)	RR 0.34 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.01 to 8.22	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Vomiting** 0/199 (0%) with oral misoprostol (600 micrograms) 1/200 (0.5%) with oxytocin (10 IU iv)	RR 0.34 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.01 to 8.17	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Diarrhoea** 1/424 (0.2%) with oral misoprostol (400 micrograms) 0/439 (0%) with oxytocin (10 IU im)	RR 3.11 95% CI 0.13 to 76.03	⟷	Not significant
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Diarrhoea** 35/9227 (0.4%) with oral misoprostol (600 micrograms) 8/9232 (0.1%) with oxytocin (10 IU im/iv)	RR 4.38 95% CI 2.03 to 9.43	●●○	oxytocin
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Diarrhoea** 1/730 (0.1%) with oral misoprostol (400 micrograms) 0/617 (0%) with oxytocin (10 IU iv)	RR 1.24 for oral misoprostol *v* oxytocin 95% CI 0.10 to 62.15	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Diarrhoea** 5/221 (2%) with oral misoprostol (800 micrograms) 0/218 (0%) with oxytocin (10 IU im)	RR 10.85 95% CI 0.60 to 195.06	⟷	Not significant
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Diarrhoea** 2/146 (1%) with oral misoprostol (400 micrograms) 5/156 (3%) with oxytocin (10 IU iv)	RR 0.43 95% 0.08 to 2.17	⟷	Not significant
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Diarrhoea** 7/247 (3%) with oral misoprostol (600 micrograms) 2/249 (1%) with oxytocin (10 IU im)	RR 3.53 95% CI 0.74 to 16.82	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Diarrhoea** 15/388 (4%) with oral misoprostol (400 micrograms) 12/384 (3%) with oxytocin (10 IU iv)	RR 1.24 95% 0.59 to 2.61	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Diarrhoea** 0% with oral misoprostol (400 micrograms) 0% with oxytocin (10 IU iv) Absolute numbers not reported			
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Diarrhoea** 4/199 (2%) with oral misoprostol (600 micrograms) 0/200 (0%) with oxytocin (10 IU iv)	RR 9.04 for misoprostol 600 micrograms *v* oxytocin 9% CI 0.49 to 166.9	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Shivering					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Shivering** 79/424 (19%) with oral misoprostol (400 micrograms) 31/439 (7%) with oxytocin (10 IU im)	RR 2.64 95% CI 1.78 to 3.91	●●○	oxytocin
[19] Systematic review	622 women with vaginal delivery in Canada Data from 1 RCT	**Shivering** 21/311 (7%) with oral misoprostol (400 micrograms) 0/311 (0%) with oxytocin (5 IU im)	RR 43.0 95% CI 2.62 to 706.74	●●●	oxytocin
[41] RCT	56 women with caesarean delivery in Switzerland Data from 1 RCT	**Shivering** 10/28 (36%) with oral misoprostol (800 micrograms) 2/25 (8%) with oxytocin (20 IU) All women received an initial bolus of oxytocin 5 IU	RR 4.46 95% CI 1.08 to 18.45	●●○	oxytocin
[19] Systematic review	40 women with elective or emergency caesarean (UK) Data from 1 RCT	**Severe shivering** 4/20 (20%) with oral misoprostol (500 micrograms) 0/20 (0%) with oxytocin (10 IU iv)	RR 9.00 95% CI 0.52 to 156.91	⟷	Not significant
[19] Systematic review	40 women with elective or emergency caesarean (UK) Data from 1 RCT	**Shivering** 13/20 (65%) with oral misoprostol (500 micrograms) 8/20 (40%) with oxytocin (10 IU iv)	RR 1.63 95% CI 0.87 to 3.04	⟷	Not significant
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Shivering** 106/243 (44%) with oral misoprostol (400 micrograms) 78/256 (22%) with oxytocin (10 IU im)	RR 1.43 95% CI 1.13 to 1.81	●○○	oxytocin
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Shivering** 1620/9227 (18%) with oral misoprostol (600 micrograms) 466/9232 (5%) with oxytocin (10 IU im/iv)	RR 3.48 95% CI 3.15 to 3.84	●●○	oxytocin
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Severe shivering** 120/9227 (1%) with oral misoprostol (600 micrograms) 14/9232 (0.2%) with oxytocin (10 IU im/iv)	RR 8.58 95% CI 4.93 to 14.91	●●●	oxytocin
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Shivering** 66/86 (77%) with oral misoprostol (600 micrograms) 38/94 (40%) with oxytocin (2.5 IU iv)	RR 11.59 95% CI 0.65 to 208.12	⟷	Not significant
[19] Systematic review	401 women with vaginal delivery in Ghana Data from 1 RCT	**Shivering** 39/176 (22%) with oral misoprostol (400 micrograms)	RR 3.90 95% CI 2.01 to 7.57	●●○	oxytocin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		10/176 (6%) with oxytocin (10 IU iv)			
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Shivering** 68/730 (9%) with oral misoprostol (400 micrograms) 14/617 (2%) with oxytocin (10 IU iv)	RR 4.11 for oral misoprostol *v* oxytocin 95% CI 2.33 to 7.22	●●○	oxytocin
[19] Systematic review **3-armed trial**	2023 women with vaginal delivery in India Data from 1 RCT Remaining arm evaluated iv ergometrine	**Severe shivering** 2/730 (0.3%) with oral misoprostol (400 micrograms) 0/617 (0%) with oxytocin (10 IU iv)	RR 4.23 for oral misoprostol *v* oxytocin 95% CI 0.20 to 87.88	⟷	Not significant
[19] Systematic review	450 women with vaginal delivery in Ghana Data from 1 RCT	**Shivering** 180/223 (80%) with oral misoprostol (800 micrograms) 8/223 (4%) with oxytocin (10 IU im)	RR 22.50 95% CI 11.36 to 44.56	●●●	oxytocin
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Shivering** 141/247 (57%) with oral misoprostol (600 micrograms) 35/249 (14%) with oxytocin (10 IU im)	RR 4.06 95% CI 2.93 to 5.62	●●○	oxytocin
[19] Systematic review	496 women with vaginal delivery in Nigeria Data from 1 RCT	**Severe shivering** 3/247 (1%) with oral misoprostol (600 micrograms) 1/249 (0.4%) with oxytocin (10 IU im)	RR 3.02 95% CI 0.32 to 28.88	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Shivering** 44/388 (11%) with oral misoprostol (400 micrograms) 19/384 (5%) with oxytocin (10 IU iv)	RR 2.29 95% CI 1.36 to 3.85	●●○	oxytocin
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Shivering** 38/198 (19%) with oral misoprostol (400 micrograms) 25/200 (13%) with oxytocin (10 IU iv)	RR 1.54 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.96 to 2.44	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Severe shivering** 0% with oral misoprostol (400 micrograms) 0% with oxytocin (10 IU iv) Absolute numbers not reported			
[19] Systematic review	597 women with vaginal delivery Data from 1 RCT	**Shivering** 56/199 (28%) with oral misoprostol (600 micrograms)	RR 2.25 for misoprostol 600 micrograms *v* oxytocin 95% CI 1.47 to 3.46	●●○	oxytocin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	Remaining arm evaluated misoprostol (400 micrograms)	25/200 (13%) with oxytocin (10 IU iv)			
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Severe shivering** 3/199 (2%) with oral misoprostol (600 micrograms) 0/200 (0%) with oxytocin (10 IU iv)	RR 7.04 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.37 to 135.32	⟷	Not significant
Fever					
[19] Systematic review	500 women with vaginal delivery in Zimbabwe Data from 1 RCT	**Fever (at least 38°C)** 18/243 (7%) with oral misoprostol (400 micrograms) 1/256 (0.4%) with oxytocin (10 IU im)	RR 18.96 95% CI 2.55 to 140.96	●●●	oxytocin
[19] Systematic review	18,530 women with vaginal delivery Data from 1 RCT	**Fever (at least 38°C)** 559/9198 (6%) with oral misoprostol (600 micrograms) 78/9205 (1%) with oxytocin (10 IU im/iv)	RR 7.17 95% CI 5.67 to 9.07	●●●	oxytocin
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (400 micrograms)	**Fever (at least 38°C)** 15/199 (8%) with oral misoprostol (600 micrograms) 6/199 (3%) with oxytocin (10 IU iv)	RR 2.5 for misoprostol 600 micrograms *v* oxytocin 95% CI 0.99 to 6.31	⟷	Not significant
[19] Systematic review **3-armed trial**	597 women with vaginal delivery Data from 1 RCT Remaining arm evaluated misoprostol (600 micrograms)	**Fever (at least 38°C)** 4/195 (2%) with oral misoprostol (400 micrograms) 6/199 (3%) with oxytocin (10 IU iv)	RR 0.68 for misoprostol 400 micrograms *v* oxytocin 95% CI 0.19 to 2.37	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Fever (at least 38°C)** 17/388 (4%) with oral misoprostol (400 micrograms) 5/384 (1%) with oxytocin (10 IU iv)	RR 3.36 95% CI 2.55 to 140.96	●●○	oxytocin
[19] Systematic review	602 women with vaginal delivery in France Data from 1 RCT	**Fever (at least 38°C)** 6/186 (3%) with oral misoprostol (600 micrograms) 0/196 (0%) with oxytocin (2.5 IU iv)	RR 13.70 95% CI 0.78 to 241.41	⟷	Not significant

Oral misoprostol versus oxytocin plus ergot compounds:

We found one systematic review (search date 2007; 3 RCTs) [19] comparing oral misoprostol versus oxytocin plus ergometrine. We also found one additional RCT. [42]

Postpartum haemorrhage

Compared with oxytocin/ergometrine combinations We don't know how oral misoprostol and oxytocin/ergometrine combinations compare at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) or severe postpartum haemorrhage (defined as blood loss of at least 1000 mL). However, oral misoprostol and oxytocin/ergometrine combinations seem equally effective at reducing the need for blood transfusion (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 12/296 (4%) with oral misoprostol (400 micrograms) 7/310 (2%) with oxytocin (5 IU iv) plus ergometrine (0.5 mg)	RR 1.80 95% CI 0.72 to 4.50	⟷	Not significant
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 5/1026 (0.5%) with oral misoprostol (600 micrograms) 4/1032 (0.4%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 1.26 95% CI 0.34 to 4.67	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 14/388 (4%) with oral misoprostol (400 micrograms) 5/398 (1%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 2.87 95% CI 1.04 to 7.90	●●○	oxytocin plus methylergometrine
[42] RCT	355 women in Hong Kong	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 2/178 (1%) with oral misoprostol (400 micrograms) 1/177 (0.6%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 1.99 95% CI 0.18 to 21.74	⟷	Not significant
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 61/296 (21%) with oral misoprostol (400 micrograms) 23/310 (7%) with oxytocin (5 IU iv) plus ergometrine (0.5 mg)	RR 2.78 95% CI 1.77 to 4.37	●●○	oxytocin plus ergometrine
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 60/1026 (6%) with oral misoprostol (600 micrograms) 44/1032 (4%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 1.37 95% CI 0.94 to 2.00	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 35/388 (9%) with oral misoprostol (400 micrograms) 14/398 (4%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 2.56 95% CI 1.40 to 4.69	●●○	oxytocin plus methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] RCT	355 women in Hong Kong	**Postpartum haemorrhage (blood loss of at least 500 mL)** 18/178 (10%) with oral misoprostol (400 micrograms) 9/177 (5%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 1.99 95% CI 0.92 to 4.31	⟷	Not significant
Blood transfusion					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Blood transfusion** 4/296 (1%) with oral misoprostol (400 micrograms) 3/310 (1%) with oxytocin (5 IU iv) plus ergometrine (0.5 mg)	RR 1.40 95% CI 0.23 to 6.19	⟷	Not significant
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Blood transfusion** 15/1026 (2%) with oral misoprostol (600 micrograms) 16/1032 (2%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 0.94 95% CI 0.47 to 1.90	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Blood transfusion** 14/388 (4%) with oral misoprostol (400 micrograms) 6/398 (2%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 2.39 95% CI 0.93 to 6.16	⟷	Not significant
[42] RCT	355 women with vaginal delivery in Hong Kong	**Blood transfusion** 8/178 (5%) with oral misoprostol (400 micrograms) 4/177 (2%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 1.99 95% CI 0.61 to 6.49	⟷	Not significant

Need for additional medical treatment

Compared with oxytocin/ergometrine combinations Oral misoprostol is less effective than oxytocin/ergometrine combinations at reducing the need for additional uterotonics (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	930 women with vaginal delivery in Australia Data from 1 RCT	**Additional uterotonics** 59/296 (20%) with oral misoprostol (400 micrograms) 23/310 (9%) with oxytocin (5 IU iv) plus ergometrine (0.5 mg)	RR 2.21 95% CI 1.45 to 3.36	●●○	oxytocin plus ergometrine
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Additional uterotonics** 232/1026 (23%) with oral misoprostol (600 micrograms) 144/1032 (14%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 1.62 95% CI 1.34 to 1.96	●○○	oxytocin plus ergometrine
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Additional uterotonics** 42/388 (10%) with oral misoprostol (400 micrograms)	RR 3.31 95% CI 1.81 to 6.08	●●○	oxytocin plus methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		13/398 (3%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)			
[42] RCT	355 women with vaginal delivery in Hong Kong	**Additional uterotonics** 41/178 (23%) with oral misoprostol (400 micrograms) 24/177 (13%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 1.70 95% CI 1.07 to 2.69	●○○	oxytocin plus ergometrine

Need for additional surgical treatment

Compared with oxytocin/ergometrine combinations We don't know how oral misoprostol and oxytocin/ergometrine combinations compare at reducing the need for manual removal of the placenta (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of placenta					
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Manual removal of placenta** 4/1026 (0.4%) with oral misoprostol (600 micrograms) 14/1032 (1.4%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 0.29 95% CI 0.09 to 0.87	●●○	misoprostol
[42] RCT	355 women with vaginal delivery in Hong Kong	**Manual placenta removal** 3/178 (2%) with oral misoprostol (400 micrograms) 7/177 (4%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 0.43 95% CI 0.11 to 1.62	⟷	Not significant

Mortality

No data from the following reference on this outcome. [19]

Maternal morbidity

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Nausea** 20/1026 (2%) with oral misoprostol (600 micrograms) 27/1032 (3%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 0.81 95% CI 0.40 to 1.63	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[42] RCT	355 women in Hong Kong	**Nausea** 13/178 (7%) with oral misoprostol (400 micrograms) 16/177 (9%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 0.81 95% CI 0.40 to 1.63	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Vomiting** 4/388 (1%) with oral misoprostol (400 micrograms) 5/398 (1%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 0.82 95% CI 0.22 to 3.03	⟷	Not significant
[42] RCT	355 women in Hong Kong	**Vomiting** 7/178 (4%) with oral misoprostol (400 micrograms) 20/177 (11%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 0.35 95% CI 0.15 to 0.80	●●○	misoprostol
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Vomiting** 14/1026 (1%) with oral misoprostol (600 micrograms) 23/1032 (2%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 0.61 95% CI 0.32 to 1.18	⟷	Not significant
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Diarrhoea** 15/388 (4%) with oral misoprostol (400 micrograms) 17/398 (4%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 0.91 95% CI 0.46 to 1.79	⟷	Not significant
[42] RCT	355 women in Hong Kong	**Diarrhoea** 0% with oral misoprostol (400 micrograms) 0% with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])			
Shivering					
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Shivering** 310/1026 (30%) with oral misoprostol (600 micrograms) 102/1032 (10%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 3.06 95% CI 2.49 to 3.76	●●○	oxytocin plus ergometrine
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Shivering** 44/388 (11%) with oral misoprostol (400 micrograms) 15/398 (4%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 3.01 95% CI 1.70 to 5.32	●●○	oxytocin plus methylergometrine
[42] RCT	355 women in Hong Kong	**Shivering** 35/178 (20%) with oral misoprostol (400 micrograms) 2/177 (1%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 17.4 95% CI 4.25 to 71.25	●●●	oxytocin plus ergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Fever					
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Fever (at least 38°C)** 87/1026 (9%) with oral misoprostol (600 micrograms) 13/1032 (1%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 6.73 95% CI 3.78 to 11.98	●●●	oxytocin plus ergometrine
[19] Systematic review	1800 women with vaginal delivery in Turkey Data from 1 RCT	**Fever (at least 38°C)** 17/388 (4%) with oral misoprostol (400 micrograms) 6/398 (2%) with oxytocin (10 IU iv) plus methylergometrine (1 mL im)	RR 2.91 95% CI 1.16 to 7.29	●●○	oxytocin plus methylergometrine
[42] RCT	355 women in Hong Kong	**Fever (at least 38°C)** 7/178 (4%) with oral misoprostol (400 micrograms) 0/177 (0%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 14.92 95% CI 0.86 to 259.21	⟷	Not significant
Headache					
[19] Systematic review	2058 women with vaginal delivery in Hong Kong Data from 1 RCT	**Headache** 81/1026 (8%) with oral misoprostol (600 micrograms) 83/1032 (8%) with oxytocin (5 IU im) plus ergometrine (0.5 mg)	RR 0.98 95% CI 0.71 to 1.35	⟷	Not significant
[42] RCT	355 women in Hong Kong	**Headache** 8/178 (5%) with oral misoprostol (400 micrograms) 2/177 (1%) with syntometrine (1-mL oxytocin [5 IU] plus ergometrine [0.5 mg])	RR 4.12 95% CI 0.86 to 19.67	⟷	Not significant

Further information on studies

[19] **Oral misoprostol versus placebo/no intervention** Two RCTs assessed 400 micrograms and 6 RCTs assessed 600 micrograms of oral misoprostol (1 RCT had separate arms for each dose). Of the RCTs included in the review, three were performed in South Africa, one in Switzerland, one in France, and one in India. Three RCTs seem to be in low-risk populations, and risk status was not clearly specified in three RCTs. The seventh RCT included in the review was conducted in Gambia. It used oral ergometrine as a control group, which was considered "no intervention" as it is not thought to be effective. Although useful as an efficacy comparison, as it is thought not to have an effect in preventing postpartum haemorrhage, it is likely to have noticeable adverse effects.

[39] The report assessing adverse effects found no significant difference between oral misoprostol and placebo in nausea, vomiting, or diarrhoea at 2 or 24 hours (P >0.05 for all outcomes at both time frames).

Comment:

Clinical guide:
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration (must be kept at <26°C), potentially making it ideal for low-resource settings. Unfortunately, although oral misoprostol seemed similar to the other interventions included here, it may be no more effective than placebo, and with significant adverse effects. Oral misoprostol is not registered for these obstetric uses and is generally unavailable in Africa and many other regions.

OPTION MISOPROSTOL (RECTAL)

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Misoprostol seems ineffective compared with placebo when administered rectally, but may be equivalent to oxytocin; this inconsistency means we are unable to judge its effectiveness.
- Rectal misoprostol is associated with adverse effects including shivering and fever.

Benefits and harms

Rectal misoprostol versus placebo/no intervention:

We found one systematic review (search date 2007) comparing prostaglandin analogues versus placebo/no intervention, which included a subgroup analysis for rectal misoprostol (1 RCT). [19]

Postpartum haemorrhage

Compared with placebo/no intervention Rectal misoprostol is no more effective than placebo or no intervention at reducing severe postpartum haemorrhage, defined as blood loss of at least 1000 mL (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 13/270 (5%) with rectal misoprostol (400 micrograms) 19/272 (7%) with placebo	RR 0.69 95% CI 0.35 to 1.37	⟷	Not significant

Need for additional medical treatment

Compared with placebo/no intervention Rectal misoprostol is no more effective than placebo or no intervention at reducing the need for additional medical treatment (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Additional medical treatment** 9/271 (3%) with rectal misoprostol (400 micrograms) 13/275 (5%) with placebo	RR 0.70 95% CI 0.31 to 1.62	⟷	Not significant

Need for additional surgical treatment

Compared with placebo/no intervention Rectal misoprostol seems no more effective than placebo or no intervention at reducing the need for manual removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of placenta					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Manual removal of placenta** 1/271 (0.3%) with rectal misoprostol (400 micrograms) 0/275 (0%) with placebo	Significance not assessed		

Mortality

No data from the following reference on this outcome. [19]

Maternal morbidity

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Vomiting** 1/271 (0.4%) with rectal misoprostol (400 micrograms) 1/275 (0.4%) with placebo	RR 1.01 95% CI 0.06 to 16.14	⟷	Not significant
Abdominal pain					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Abdominal pain** 1/271 (0.4%) with rectal misoprostol (400 micrograms) 0/275 (0%) with placebo	RR 3.04 95% CI 0.12 to 74.40	⟷	Not significant
Shivering					
[19] Systematic review	550 low-risk women in South Africa Data from 1 RCT	**Shivering** 1/34 (3%) with rectal misoprostol (400 micrograms) 4/36 (11%) with placebo	RR 0.26 95% CI 0.03 to 2.25	⟷	Not significant

Rectal misoprostol versus oxytocin:

We found one systematic review [19] (search date 2007; 4 RCTs) and one subsequent RCT [43] comparing rectal misoprostol versus oxytocin.

Postpartum haemorrhage

Compared with oxytocin Rectal misoprostol and oxytocin are equally effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL), reducing severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), and reducing the need for transfusion (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 17/396 (4%) with rectal misoprostol (400 micrograms) 14/407 (3%) with oxytocin (10 IU iv)	RR 1.25 95% CI 0.62 to 2.50	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)**	RR 0.35 95% CI 0.01 to 8.56	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	0/323 (0%) with rectal misoprostol (400 micrograms) 1/339 (0.3%) with oxytocin (10 IU im)			
[19] Systematic review	400 women with vaginal delivery in the US Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 15/154 (10%) with rectal misoprostol (400 micrograms) 14/161 (9%) with oxytocin (20 IU)	RR 1.12 95% CI 0.56 to 2.24	⟷	Not significant
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 33/396 (8%) with rectal misoprostol (400 micrograms) 33/407 (8%) with oxytocin (10 IU iv)	RR 1.03 95% CI 0.65 to 1.63	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 10/323 (3%) with rectal misoprostol (400 micrograms) 15/339 (4%) with oxytocin (10 IU im)	RR 0.70 95% CI 0.32 to 1.53	⟷	Not significant
[19] Systematic review	400 women with vaginal delivery in the US Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 70/154 (45%) with rectal misoprostol (400 micrograms) 61/161 (38%) with oxytocin (20 IU)	RR 1.20 95% CI 0.92 to 1.56	⟷	Not significant
[43] RCT	514 women with vaginal delivery in Egypt	**Postpartum haemorrhage (blood loss of at least 500 mL)** 17/257 (7%) with rectal misoprostol (800 micrograms) 12/257 (5%) with oxytocin (5 IU iv)	RR 1.42 95% CI 0.69 to 2.91	⟷	Not significant
Blood transfusion					
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Blood transfusion** 12/396 (3%) with rectal misoprostol (400 micrograms) 13/407 (3%) with oxytocin (10 IU iv)	RR 0.95 95% CI 0.44 to 2.05	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Blood transfusion** 2/323 (0.6%) with rectal misoprostol (400 micrograms) 1/339 (0.3%) with oxytocin (10 IU im)	RR 2.10 95% CI 0.19 to 23.04	⟷	Not significant
[19] Systematic review	400 women with vaginal delivery in the US Data from 1 RCT	**Blood transfusion** 2/159 (1%) with rectal misoprostol (400 micrograms) 2/166 (1%) with oxytocin (20 IU)	RR 1.04 95% CI 0.15 to 7.32	⟷	Not significant
[19] Systematic review	223 women with vaginal delivery in Canada	**Blood transfusion** 0/110 (0%) with rectal misoprostol (400 micrograms)	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT	0/113 (0%) with oxytocin (10 IU iv or im)			
[43] RCT	514 women with vaginal delivery in Egypt	**Blood transfusion** 8/257 (3%) with rectal misoprostol (800 micrograms) 4/257 (1.6%) with oxytocin (5 IU iv)	RR 2.2 95% CI 0.40 to 6.20	⟷	Not significant

Need for additional medical treatment

Compared with oxytocin Rectal misoprostol and oxytocin seem equally effective at reducing the need for additional uterotonics (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Additional uterotonics** 28/110 (25%) with rectal misoprostol (400 micrograms) 20/113 (18%) with oxytocin (10 IU iv or im)	RR 1.44 95% CI 0.86 to 2.40	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Additional uterotonics** 7/323 (2%) with rectal misoprostol (400 micrograms) 7/339 (2%) with oxytocin (10 IU im)	RR 1.05 95% CI 0.37 to 2.96	⟷	Not significant
[19] Systematic review	400 women with vaginal delivery in the US Data from 1 RCT	**Additional uterotonics** 36/159 (23%) with rectal misoprostol (400 micrograms) 18/166 (11%) with oxytocin (20 IU)	RR 2.09 95% CI 1.24 to 3.52	●●○	oxytocin
[43] RCT	514 women with vaginal delivery in Egypt	**Additional uterotonics** 6/257 (2.3%) with rectal misoprostol (800 micrograms) 4/257 (1.6%) with oxytocin (5 IU iv)	RR 1.50 95% CI 0.46 to 4.91	⟷	Not significant

Need for additional surgical treatment

Compared with oxytocin Rectal misoprostol and oxytocin seem equally effective at reducing the need for manual removal of the placenta (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Manual removal of placenta					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Manual removal of placenta** 1/110 (0.9%) with rectal misoprostol (400 micrograms) 6/113 (5%) with oxytocin (10 IU iv or im)	RR 0.17 95% CI 0.02 to 1.40	⟷	Not significant

No data from the following reference on this outcome. [43]

Mortality

No data from the following reference on this outcome. [19] [43]

Maternal morbidity

No data from the following reference on this outcome. [19] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Nausea** 8/105 (8%) with rectal misoprostol (400 micrograms) 5/110 (5%) with oxytocin (10 IU iv or im)	RR 1.68 95% CI 0.57 to 4.96	⟷	Not significant
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Vomiting** 6/105 (6%) with rectal misoprostol (400 micrograms) 4/110 (4%) with oxytocin (10 IU iv or im)	RR 1.57 95% CI 0.46 to 5.14	⟷	Not significant
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Vomiting** 2/396 (0.5%) with rectal misoprostol (400 micrograms) 2/407 (0.5%) with oxytocin (10 IU iv)	RR 1.03 95% CI 0.15 to 7.26	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Vomiting** 2/323 (0.6%) with rectal misoprostol (400 micrograms) 1/337 (0.3%) with oxytocin (10 IU im)	RR 2.09 95% CI 0.19 to 22.90	⟷	Not significant
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Diarrhoea** 11/396 (3%) with rectal misoprostol (400 micrograms) 9/407 (2%) with oxytocin (10 IU iv)	RR 1.26 95% CI 0.53 to 3.00	⟷	Not significant
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Diarrhoea** 0/323 (0%) with rectal misoprostol (400 micrograms) 2/338 (0.6%) with oxytocin (10 IU im)	RR 0.21 95% CI 0.01 to 4.34	⟷	Not significant
[43] RCT	514 women with vaginal delivery in Egypt	**Diarrhoea** 6/257 (2.2%) with rectal misoprostol (800 micrograms) 5/257 (2.0%) with oxytocin (5 IU iv)	RR 1.2 95% CI 0.4 to 3.7	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Abdominal pain					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Abdominal pain** 12/105 (11%) with rectal misoprostol (400 micrograms) 13/110 (12%) with oxytocin (10 IU iv or im)	RR 0.97 95% CI 0.46 to 2.02	⟷	Not significant
Shivering					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Shivering** 26/105 (25%) with rectal misoprostol (400 micrograms) 15/110 (14%) with oxytocin (10 IU iv or im)	RR 1.82 95% CI 1.02 to 3.23	●○○	oxytocin
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Shivering** 47/396 (12%) with rectal misoprostol (400 micrograms) 16/407 (4%) with oxytocin (10 IU iv)	RR 3.02 95% CI 1.74 to 5.23	●●○	oxytocin
[19] Systematic review	633 women with vaginal delivery in Mozambique Data from 1 RCT	**Shivering** 113/323 (38%) with rectal misoprostol (400 micrograms) 51/337 (15%) with oxytocin (10 IU im)	RR 2.52 95% CI 1.89 to 3.36	●●○	oxytocin
[19] Systematic review	400 women with vaginal delivery in the US Data from 1 RCT	**Shivering** 7/159 (4%) with rectal misoprostol (400 micrograms) 7/166 (4%) with oxytocin (20 IU)	RR 1.04 95% CI 0.37 to 2.91	⟷	Not significant
[43] RCT	514 women with vaginal delivery in Egypt	**Shivering** 80/257 (31%) with rectal misoprostol (800 micrograms) 0/257 (0%) with oxytocin (5 IU iv)	P <0.001	○○○	oxytocin
Fever					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Fever (at least 38°C)** 20/107 (19%) with rectal misoprostol (400 micrograms) 12/112 (11%) with oxytocin (10 IU iv or im)	RR 1.74 95% CI 0.90 to 3.39	⟷	Not significant
[19] Systematic review	1663 women with vaginal delivery in Turkey Data from 1 RCT	**Fever (at least 38°C)** 16/396 (4%) with rectal misoprostol (400 micrograms) 6/407 (2%) with oxytocin (10 IU iv)	RR 2.47 95% CI 1.08 to 6.93	●●○	oxytocin
[43] RCT	514 women with vaginal delivery in Egypt	**Fever** 48/257 (19%) with rectal misoprostol (800 micrograms) 2/257 (1%) with oxytocin (5 IU iv)	P <0.001	○○○	oxytocin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache					
[19] Systematic review	223 women with vaginal delivery in Canada Data from 1 RCT	**Headache** 9/105 (9%) with rectal misoprostol (400 micrograms) 4/100 (4%) with oxytocin (10 IU iv or im)	RR 2.36 95% CI 0.75 to 7.42	⟷	Not significant

Rectal misoprostol versus oxytocin plus ergot alkaloids:

We found one systematic review (search date 2007; 2 RCTs) comparing rectal misoprostol versus oxytocin plus ergot compounds. [19]

Postpartum haemorrhage

Compared with oxytocin plus ergometrine combinations Rectal misoprostol seems more effective than oxytocin plus ergometrine combinations at reducing severe postpartum haemorrhage (defined as blood loss of at least 1000 mL), but as effective as oxytocin plus ergometrine combinations at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL) and at reducing the need for blood transfusions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Severe postpartum haemorrhage (blood loss of at least 1000 mL)** 17/396 (4%) with rectal misoprostol (400 micrograms) 7/402 (2%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 2.47 95% CI 1.03 to 5.88	●●○	oxytocin plus methylergometrine
[19] Systematic review	491 women at low risk of postpartum haemorrhage in South Africa Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 2/231 (0.9%) with rectal misoprostol (400 micrograms) 1/233 (0.4%) with syntometrine (ergometrine plus oxytocin [1 ampoule im])	RR 2.02 95% CI 0.18 to 22.09	⟷	Not significant
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 39/396 (10%) with rectal misoprostol (400 micrograms) 14/402 (4%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 2.83 95% CI 1.56 to 5.13	●●○	oxytocin plus methylergometrine
Blood transfusion					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Blood transfusion** 12/396 (3%) with rectal misoprostol (400 micrograms) 4/402 (1%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 3.11 95% CI 0.99 to 9.72	⟷	Not significant

Need for additional medical treatment

Compared with oxytocin plus ergometrine combinations Rectal misoprostol is less effective at reducing the need for additional uterotonics (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Additional uterotonics** 51/396 (12%) with rectal misoprostol (400 micrograms) 15/402 (4%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 3.45 95% CI 1.97 to 6.03	●●○	oxytocin plus methylergometrine

Mortality

No data from the following reference on this outcome. [19]

Maternal morbidity

No data from the following reference on this outcome. [19]

Need for additional surgical treatment

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Vomiting** 2/396 (0.5%) with rectal misoprostol (400 micrograms) 1/402 (0.2%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 2.03 95% CI 0.18 to 22.30	⟷	Not significant
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Diarrhoea** 11/396 (3%) with rectal misoprostol (400 micrograms) 10/402 (3%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 1.12 95% CI 0.48 to 2.60	⟷	Not significant
Shivering					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Shivering** 47/396 (12%) with rectal misoprostol (400 micrograms)	RR 2.51 95% CI 1.50 to 4.20	●●○	oxytocin plus methylergometrine

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		19/402 (5%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])			
Fever					
[19] Systematic review	793 women with vaginal delivery in Turkey Data from 1 RCT	**Fever (at least 38°C)** 16/396 (4%) with rectal misoprostol (400 micrograms) 6/402 (2%) with syntometrine (oxytocin iv [10 IU] plus methylergometrine im [1 mL])	RR 2.71 95% CI 1.04 to 6.85	●●○	oxytocin plus methylergometrine

Rectal misoprostol versus carboprost injection:

We found one systematic review (search date 2007), [19] which identified one RCT.

Postpartum haemorrhage

Compared with carboprost injection Rectal misoprostol and carboprost injection may be equally effective at reducing postpartum haemorrhage (defined as blood loss of at least 500 mL), but we don't know how they compare at reducing the need for blood transfusion (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Postpartum haemorrhage					
[19] Systematic review	120 full-term low-risk women in rural India Data from 1 RCT	**Postpartum haemorrhage (blood loss of at least 500 mL)** 4/60 (0.6%) with rectal misoprostol (400 micrograms) 3/60 (0.6%) with prostaglandin F2-alpha (15-methyl prostaglandin F2-alpha [125 micrograms])	RR 1.33 95% CI 0.31 to 5.70	⟷	Not significant
Blood transfusion					
[19] Systematic review	120 full-term low-risk women in rural India Data from 1 RCT	**Blood transfusion** 1/60 (2%) with rectal misoprostol (400 micrograms) 0/60 (0%) with prostaglandin F2-alpha (15-methyl prostaglandin F2-alpha [125 micrograms])	Significance not assessed		

Need for additional medical treatment

Compared with carboprost injection Rectal misoprostol is less effective than carboprost injection at reducing the need for additional uterotonics (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Additional medical treatment					
[19] Systematic review	120 full-term low-risk women in rural India Data from 1 RCT	**Additional oxytocics** 10/60 (17%) with rectal misoprostol (400 micrograms) 2/60 (3%) with prostaglandin F2-alpha (15-methyl prostaglandin F2-alpha [125 micrograms])	RR 5.0 95% CI 1.14 to 21.86	●●●	prostaglandin F2-alpha

Mortality

No data from the following reference on this outcome. [19]

Maternal morbidity

No data from the following reference on this outcome. [19]

Need for additional surgical treatment

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Gastrointestinal effects					
[19] Systematic review	120 full-term low-risk women in rural India Data from 1 RCT	**Gastrointestinal adverse effects** 3/60 (5%) with rectal misoprostol (400 micrograms) 11/60 (18%) with prostaglandin F2-alpha (15-methyl prostaglandin F2-alpha [125 micrograms]) Gastrointestinal adverse effects included nausea, vomiting, and diarrhoea	RR 0.27 95% CI 0.08 to 0.93	●●○	misoprostol
Shivering					
[19] Systematic review	120 full-term low-risk women in rural India Data from 1 RCT	**Shivering** 5/60 (8%) with rectal misoprostol (400 micrograms) 0/60 (0%) with prostaglandin F2-alpha (15-methyl prostaglandin F2-alpha [125 micrograms])	P = 0.06	⟷	Not significant

Further information on studies

Comment: **Clinical guide:**
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration, potentially making it ideal for low-resource settings. Unfortunately, rectally administered misoprostol is less effective than other interventions, and seems no more effective than placebo, with significant adverse effects.

OPTION MISOPROSTOL (VAGINAL)

- For GRADE evaluation of interventions for Postpartum haemorrhage: prevention, see table, p 107 .
- Misoprostol seems ineffective compared with placebo when administered vaginally, and is associated with adverse effects including shivering and fever.

Benefits and harms

Vaginal misoprostol versus placebo/no intervention:

We found one RCT comparing misoprostol administered vaginally versus placebo. [44]

Postpartum haemorrhage

Compared with placebo/no intervention We don't know whether vaginal misoprostol is more effective than placebo or no intervention at reducing blood loss (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Blood loss (volume)					
[44] RCT **3-armed trial**	100 women delivering after 32 weeks' gestation The remaining arm evaluated rectal misoprostol	**Estimated blood loss** 206 mL with vaginal misoprostol (400 micrograms) 171 mL with placebo	Significance not assessed		
Postpartum haemoglobin/haematocrit level					
[44] RCT **3-armed trial**	100 women delivering after 32 weeks' gestation The remaining arm evaluated rectal misoprostol	**Haemoglobin levels , 24 hours postpartum** 11.1 g/dL with vaginal misoprostol (400 micrograms) 11.6 g/dL with placebo	Significance not assessed		
[44] RCT **3-armed trial**	100 women delivering after 32 weeks' gestation The remaining arm evaluated rectal misoprostol	**Change in haemoglobin , 24 hours postpartum** 1 g/dL with vaginal misoprostol (400 micrograms) 1 g/dL with placebo	Significance not assessed		

Mortality

No data from the following reference on this outcome. [44]

Maternal morbidity

No data from the following reference on this outcome. [44]

Need for additional medical treatment

No data from the following reference on this outcome. [44]

Need for additional surgical treatment

No data from the following reference on this outcome. [44]

Adverse effects

No data from the following reference on this outcome. [44]

Further information on studies

Comment: **Clinical guide:**
Misoprostol has been studied with great excitement because it is inexpensive, easily administered, and does not require strict refrigeration, potentially making it ideal for low-resource settings. Limited evidence is available regarding vaginally administered misoprostol. The single available study showed no difference from placebo.

GLOSSARY

Active management Management of the third stage of labour through a combination of interventions, usually including: immediate cord clamping, cutting, and drainage; controlled cord traction; and use of an oxytocic agent (oxytocin, a fixed combination of oxytocin plus ergometrine, ergot compound, etc.).

Ergot compounds Naturally occurring alkaloids that cause uterine contraction. Available for clinical use as ergometrine, methylergonovine, and methergine.

Expectant management Management of the third stage by passive means. No active interventions such as oxytocic administration or cord traction are used. In general, the placenta is allowed to be delivered by a combination of gravity and natural uterine contractions, sometimes in conjunction with nipple stimulation.

Oxytocic agent Any agent that makes the uterus contract.

Oxytocin Peptide hormone endogenously synthesised in the hypothalamus (supraoptic and paraventricular nuclei) and released from the posterior pituitary, and important for uterine contractility. Given either intramuscularly or intravenously for the induction or augmentation of labour, and the prevention or treatment of postpartum haemorrhage.

Retained placental tissue Placenta that has not been delivered within a specified length of time, often 30 minutes, from time of the delivery of the baby.

Controlled cord traction A technique that involves applying traction to the umbilical cord after the uterus has begun to contract. This can be done constantly or intermittently, usually every few minutes.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Sheehan's syndrome A condition caused by necrosis of the pituitary gland with associated hypopituitarism, resulting from severe postpartum haemorrhage. Although it can cause hypotension and shock immediately postpartum, in most cases the onset is slower – days, weeks, or even years later. Common features are lack of lactation postpartum, amenorrhoea, loss of pubic hair, weight loss, and lethargy. Although increasingly rare in the western world, it is one of the most common causes of hypopituitarism in resource-poor countries.

Uterine massage A technique that involves manually rubbing the uterine fundus through the abdominal wall immediately after birth.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Carboprost injection New evidence added. [23] [24] Categorisation unchanged (Trade off between benefits and harms).

Controlled cord traction New evidence added. [8] Categorisation unchanged (Likely to be beneficial).

Misoprostol (oral) New evidence added. [39] [40] Categorisation changed from Likely to be ineffective or harmful to Unlikely to be beneficial to be consistent with the categorisation of vaginal misoprostol. The evidence for both oral and vaginal misoprostol is currently conflicting and meta-analyses of the data are needed to draw firmer conclusions.

Misoprostol (sublingual) New evidence added. [18] [24] [37] Categorisation changed from Unknown effectiveness to Trade off between benefits and harms.

Oxytocin New evidence added. [18] [17] Categorisation unchanged (Beneficial).

Oxytocin plus ergometrine New evidence added. [29] Categorisation unchanged (Trade off between benefits and harms).

Uterine massage New evidence added. [11] Conclusions confirmed (Likely to be beneficial).

Misoprostol (rectal) New evidence added. [43] Categorisation changed from Likely to be ineffective or harmful to Unknown effectiveness as the evidence is inconsistent: rectal misoprostol seems no more effective than placebo but may possibly be equivalent to oxytocin; we are therefore unable to draw conclusions on its effectiveness.

REFERENCES

1. World Health Organization. Making pregnancy safer. Reducing the global burden: postpartum haemorrhage. 2007. Available at: http://www.who.int/making_pregnancy_safer/documents/newsletter/mps_newsletter_issue4.pdf (last accessed 25 February 2011).
2. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006;367:1066−1074.[PubMed]
3. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance − United States, 1991−1999. *MMWR Surveill Summ* 2003;52:1−8.[PubMed]
4. Prendiville WJ, Elbourne D, McDonald S. Active versus expectant management in the third stage of labour. In: The Cochrane Library, Issue 3, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2000.
5. Althabe F, Bergel E, Buekens P, et al. Controlled cord traction in the third stage of labor. Systematic review. *Int J Gynecol Obstet* 2006;94:S126−S127.
6. Khan GQ, John IS, Wani S, et al. Controlled cord traction versus minimal intervention techniques in delivery of the placenta: a randomized controlled trial. *Am J Obstet Gynecol* 1997;177:770−774.[PubMed]
7. Zhao S, Xiaofeng S. Clinical study on curing postpartum hemorrhage in the third stage of labor. *J Pract Obstet Gynecol* 2003;19:278−280.
8. Althabe F, Aleman A, Tomasso G, et al. A pilot randomized controlled trial of controlled cord traction to reduce postpartum blood loss. *Int J Gynaecol Obstet* 2009;107:4−7.[PubMed]
9. Giacalone PL, Vignal J, Daures JP, et al. A randomised evaluation of two techniques of management of the third stage of labour in women at low risk of postpartum haemorrhage. *Br J Obstet Gynaecol* 2000;107:396−400.[PubMed]
10. Betran AP, de Onis M, Lauer JA, et al. Ecological study of effect of breast feeding on infant mortality in Latin America. *BMJ* 2001;323:303−306.[PubMed]
11. Hofmeyr GJ, Abdel-Aleem H, Abdel-Aleem MA. Uterine massage for preventing postpartum haemorrhage. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
12. Abdel-Aleem H, Hofmeyr GJ, Shokry M, et al. Uterine massage and postpartum blood loss. *Int J Gynecol Obstet* 2006;93:238−239.[PubMed]
13. Cotter A, Ness A, Tolosa J. Prophylactic oxytocin for the third stage of labour. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2004. Search updated 2009.
14. Jerbi M, Hidar S, Elmoueddeb S, et al. Oxytocin in the third stage of labor. *Int J Gynecol Obstet* 2007;96:198−199.[PubMed]
15. Moir DD, Amoa AB. Ergometrine or oxytocin? Blood loss and side-effects at spontaneous vertex delivery. *Br J Anaesth* 1979;51:113−117.[PubMed]
16. Zachariah ES, Naidu M, Seshadri L. Oral misoprostol in the third stage of labor. *Int J Gynecol Obstetr* 2006;92:23−26.[PubMed]
17. Orji E, Agwu F, Loto O, et al. A randomized comparative study of prophylactic oxytocin versus ergometrine in the third stage of labor. *Int J Gynaecol Obstet* 2008;101:129−132.[PubMed]
18. Singh G, Radhakrishnan G, Guleria K, et al. Comparison of sublingual misoprostol, intravenous oxytocin, and intravenous methylergometrine in active management of the third stage of labor. *Int J Gynaecol Obstet* 2009;107:130−134.[PubMed]
19. Gulmezoglu AM, Forna F, Villar J, et al. Prostaglandins for the prevention of postpartum haemorrhage. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
20. Abdel-Aleem H, Abol-Oyoun EM, Moustafa SA, et al. Carboprost trometamol in the management of the third stage of labor. *Int J Gynaecol Obstet* 1993;42:247−250.[PubMed]
21. Reddy R, Shenoy JV. Active management of third stage of labour. A comparative study in high risk patents for atonic postpartum haemorrhage. *J Obstet Gynecol India* 2001;51:44−47.
22. Kushtagi P, Verghese LM. Evaluation of two uterotonic medications for the management of the third stage of labor. *Int J Gynecol Obstet* 2006;94:47−48.[PubMed]
23. Biswas A, Bal R, Kundu MK, et al. A study of prophylactic use of 15-methyl prostaglandin F2alpha in the active management of third stage of labour. *J Indian Med Assoc* 2007;105:506−509.[PubMed]
24. Vaid A, Dadhwal V, Mittal S, et al. A randomized controlled trial of prophylactic sublingual misoprostol versus intramuscular methyl-ergometrine versus intramuscular 15-methyl PGF2alpha in active management of third stage of labor. *Arch Gynecol Obstet* 2009;280:893−897.[PubMed]
25. Lamont RF, Morgan DJ, Logue M, et al. A prospective randomised trial to compare the efficacy and safety of hemabate and syntometrine for the prevention of primary postpartum haemorrhage. *Prostaglandins Other Lipid Mediat* 2001;66:203−210.[PubMed]
26. Chua S, Chew SL, Yeoh CL, et al. A randomized controlled study of prostaglandin 15-methyl F2 alpha compared with syntometrine for prophylactic use in the third stage of labour. *Aust N Z J Obstet Gynaecol* 1995;35:413−416.[PubMed]
27. Liabsuetrakul T, Choobun T, Peeyananjarassri K, et al. Prophylactic use of ergot alkaloids in the third stage of labour. In: The Cochrane Library, Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.
28. McDonald S, Abbot JM, Higgins SP. Prophylactic ergometrine-oxytocin versus oxytocin for the third stage of labour. In: The Cochrane Library: Issue 2, 2010. Chichester, UK: John Wiley & Sons, Ltd. Search date 2007.
29. Rashid M, Clark A, Rashid MH, et al. A randomised controlled trial comparing the efficacy of intramuscular syntometrine and intravenous syntocinon, in preventing postpartum haemorrhage. *J Obstet Gynaecol* 2009;29:396−401.[PubMed]
30. Poeschmann RP, Doesburg WH, Eskes TK. A randomized comparison of oxytocin, sulprostone and placebo in the management of the third stage of labour. *Br J Obstet Gynaecol* 1991;98:528−530.[PubMed]
31. Van Selm M, Kanhai HH, Keirse MJ. Preventing the recurrence of atonic postpartum hemorrhage: a double-blind trial. *Acta Obstet Gynecol Scand* 1995;74:270−274.[PubMed]
32. Hoj L, Cardoso P, Nielsen BB, et al. Effect of sublingual misoprostol on severe postpartum haemorrhage in a primary health centre in Guinea-Bissau: a randomised double blind clinical trial. *BMJ* 2005;331:723−727.[PubMed]
33. Penaranda WA, Arrieta OB, Yances BR. Active management of the childbirth sublingual misoprostol: A clinical controlled trial in the Hospital de Materindad Rafael Calvo de Cartagena. *Rev Colomb Obstet Ginecol* 2002;53:87−91.
34. Vimala N, Mittal S, Kumar S. Sublingual misoprostol versus oxytocin infusion to reduce blood loss at cesarean section. *Int J Gynecol Obstet* 2006;92:106−110.[PubMed]
35. Vimala N, Mittal S, Kumar S, et al. Sublingual misoprostol versus methylergometrine for active management of the third stage of labor. *Int J Gynaecol Obstet* 2004;87:1−5.[PubMed]
36. Verma P, Aggarwal N, Jain V, et al. A double-blind randomized controlled trial to compare sublingual misoprostol with methylergometrine for prevention of postpartum hemorrhage. *Int J Gynecol Obstet* 2006;94:S137−S138.
37. Chhabra S, Tickoo C. Low-dose sublingual misoprostol versus methylergometrine for active management of the third stage of labor. *J Obstet Gynaecol Res* 2008;34:820−823.[PubMed]
38. Lam H, Tang OS, Lee CP, et al. A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in the third stage of labor. *Acta Obstet Gynecol Scand* 2004;83:647−650.[PubMed]
39. Patted SS, Goudar SS, Naik VA, et al. Side effects of oral misoprostol for the prevention of postpartum hemorrhage: results of a community-based randomised controlled trial in rural India. *J Matern Fetal Neonatal Med* 2009;22:24−28.[PubMed]
40. Enakpene CA, Morhason-Bello IO, Enakpene EO, et al. Oral misoprostol for the prevention of primary post-partum hemorrhage during third stage of labor. *J Obstet Gynaecol Res* 2007;33:810−817.[PubMed]
41. Lapaire O, Schneider MC, Stotz M, et al. Oral misoprostol vs. intravenous oxytocin in reducing blood loss after emergency cesarean delivery. *Int J Gynecol Obstet* 2006;95:2−7.[PubMed]
42. Ng PS, Lai CY, Sahota DS, et al. A double-blind randomized controlled trial of oral misoprostol and intramuscular syntometrine in the management of the third stage of labor. *Gynecol Obstet Invest* 2007;63:55−60.[PubMed]

43. Nasr A, Shahin AY, Elsamman AM, et al. Rectal misoprostol versus intravenous oxytocin for prevention of postpartum hemorrhage. *Int J Gynaecol Obstet* 2009;105:244−247.[PubMed]

44. Ozkaya O, Sezik M, Kaya H, et al. Placebo-controlled randomized comparison of vaginal with rectal misoprostol in the prevention of postpartum hemorrhage. *J Obstet Gynaecol Res* 2005:31;389−393.[PubMed]

David Chelmow
Professor and Chair, Department of Obstetrics and Gynecology
Virginia Common Wealth University Medical Centre
Richmond
USA

Competing interests: DC declares that he has no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Postpartum haemorrhage: prevention.**

Important outcomes **Adverse effects, Maternal morbidity, Mortality, Need for additional medical treatment, Need for additional surgical treatment, Postpartum haemorrhage**

Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of non-drug interventions to prevent primary postpartum haemorrhage?									
5 (6477) [4]	Postpartum haemorrhage	Active management versus expectant management or oxytocin	4	0	0	0	0	High	
5 (6477) [4]	Need for additional medical treatment	Active management versus expectant management or oxytocin	4	0	0	0	+1	High	Effect-size point added for RR <0.5
5 (6477) [4]	Need for additional surgical treatment	Active management versus expectant management or oxytocin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
5 (6477) [4]	Adverse effects	Active management versus expectant management or oxytocin	4	0	0	0	0	High	
3 (2152) [6] [7] [8]	Postpartum haemorrhage	Controlled cord traction versus minimal intervention	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for differences in timing and mode of oxytocin administration in largest RCT
2 (1852) [6] [8]	Need for additional medical treatment	Controlled cord traction versus minimal intervention	4	0	0	–1	0	Moderate	Directness point deducted for differences in timing and mode of oxytocin administration
2 (1852) [6] [8]	Need for additional surgical treatment	Controlled cord traction versus minimal intervention	4	0	0	–1	0	Moderate	Directness point deducted for differences in timing and mode of oxytocin administration
1 (477) [9]	Postpartum haemorrhage	Controlled cord traction plus immediate cord drainage versus expectant management	4	–1	–1	0	0	Low	Quality point deducted for uncertainty of timing of cord drainage. Consistency point deducted for lack of consistent benefit
1 (477) [9]	Need for additional surgical treatment	Controlled cord traction plus immediate cord drainage versus expectant management	4	0	0	0	0	High	
1 (200) [12]	Postpartum haemorrhage	Uterine massage plus active management versus active management	4	0	0	0	0	High	
1 (200) [12]	Need for additional medical treatment	Uterine massage plus active management versus active management	4	0	0	0	+1	High	Effect-size point added for RR <0.5
What are the effects of drug interventions to prevent primary postpartum haemorrhage?									
at least 7 (at least 3323) [13] [14]	Postpartum haemorrhage	Oxytocin versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of quasi-randomised trials
5 (2327) [13]	Need for additional medical treatment	Oxytocin versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for methodological issues (incomplete reporting of results, and inclusion of quasi-randomised trial in 1 analysis)

Important outcomes	Adverse effects, Maternal morbidity, Mortality, Need for additional medical treatment, Need for additional surgical treatment, Postpartum haemorrhage								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
5 (2373) [13] [14]	Need for additional surgical treatment	Oxytocin versus placebo/no intervention	4	–2	0	0	0	Low	Quality points deducted for inclusion of quasi-randomised trial and no statistical assessment between groups in 1 RCT
at least 9 (at least 5930) [13] [15] [16] [18] [17]	Postpartum haemorrhage	Oxytocin versus ergot compounds	4	–2	0	0	0	Low	Quality points deducted for inclusion of quasi-randomised trials and incomplete reporting of results
5 (4007) [13] [16] [17] [18]	Need for additional medical treatment	Oxytocin versus ergot compounds	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (3770) [13] [16]	Need for additional surgical treatment	Oxytocin versus ergot compounds	4	–2	–1	0	0	Very low	Quality points deducted for inclusion of quasi-randomised trial and incomplete reporting of results. Consistency point deducted for conflicting results
4 (545) [20] [21] [22] [23]	Postpartum haemorrhage	Carboprost injection versus ergot compounds	4	–1	0	0	0	Moderate	Quality point deducted for comparison of results from drugs given at different time points in one RCT
2 (641) [26] [25]	Postpartum haemorrhage	Carboprost injection versus oxytocin plus ergometrine	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and the inclusion of an interim analysis
2 (212) [26]	Need for additional medical treatment	Carboprost injection versus oxytocin plus ergometrine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (112) [26]	Need for additional surgical treatment	Carboprost injection versus oxytocin plus ergometrine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
at least 3 (at least 3409) [27]	Postpartum haemorrhage	Ergot compounds versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (at least 2409) [27]	Need for additional medical treatment	Ergot compounds versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (1429) [27]	Need for additional surgical treatment	Ergot compounds versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
5 (2891) [13]	Postpartum haemorrhage	Oxytocin plus ergometrine versus ergot compounds alone	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
2 (1927) [13]	Need for additional surgical treatment	Oxytocin plus ergometrine versus ergot compounds alone	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
7 (10,818) [28] [29]	Postpartum haemorrhage	Oxytocin plus ergometrine versus oxytocin alone	4	–1	0	0	0	Moderate	Quality point deducted for inclusion of controlled trial
4 (6151) [28] [29]	Need for additional medical treatment	Oxytocin plus ergometrine versus oxytocin alone	4	0	–2	0	0	Low	Consistency points deducted for significant statistical heterogeneity among RCTs and for different results with different analyses
7 (10,018) [28] [29]	Need for additional surgical treatment	Oxytocin plus ergometrine versus oxytocin alone	4	–1	–1	0	0	Low	Quality point deducted for inclusion of controlled trial. Consistency point deducted for conflicting results across trials

Important outcomes	Adverse effects, Maternal morbidity, Mortality, Need for additional medical treatment, Need for additional surgical treatment, Postpartum haemorrhage								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (46) [30]	Postpartum haemorrhage	Sulprostone injection versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (46) [30]	Need for additional medical treatment	Sulprostone injection versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (51) [30]	Postpartum haemorrhage	Sulprostone injection versus oxytocin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (51) [30]	Need for additional medical treatment	Sulprostone injection versus oxytocin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (51) [30]	Need for additional surgical treatment	Sulprostone injection versus oxytocin	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting
1 (661) [32]	Mortality	Sublingual misoprostol versus placebo/no intervention	4	–1	0	–1	0	Low	Quality point deducted for no significance assessment. Directness point deducted for low number of events
1 (661) [32]	Postpartum haemorrhage	Sublingual misoprostol versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (661) [32]	Need for additional medical treatment	Sublingual misoprostol versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (661) [32]	Need for additional surgical treatment	Sublingual misoprostol versus placebo/no intervention	2	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
3 (375) [33] [34] [18]	Postpartum haemorrhage	Sublingual misoprostol versus oxytocin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results across RCTs
1 (100) [34]	Need for additional medical treatment	Sublingual misoprostol versus oxytocin	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (133) [24]	Postpartum haemorrhage	Sublingual misoprostol versus carboprost	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for no direct pairwise comparison
1 (133) [24]	Need for additional medical treatment	Sublingual misoprostol versus carboprost	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for no direct pairwise comparison
6 (1095) [33] [35] [36] [24] [37] [18]	Postpartum haemorrhage	Sublingual misoprostol versus ergometrine	4	0	0	0	0	High	
5 (858) [35] [36] [18] [24] [37]	Need for additional medical treatment	Sublingual misoprostol versus ergometrine	4	0	0	0	0	High	
2 (320) [36] [35]	Need for additional surgical treatment	Sublingual misoprostol versus ergometrine	4	0	0	–1	0	Moderate	Directness point deducted for narrowness of population (women at low risk of haemorrhage)
1 (60) [38]	Postpartum haemorrhage	Sublingual misoprostol versus oxytocin plus ergometrine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (60) [38]	Need for additional surgical treatment	Sublingual misoprostol versus oxytocin plus ergometrine	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Important outcomes	Adverse effects, Maternal morbidity, Mortality, Need for additional medical treatment, Need for additional surgical treatment, Postpartum haemorrhage								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
2 (2849) [19]	Mortality	Oral misoprostol versus placebo/no intervention	4	0	0	0	0	High	
7 (5153) [19]	Postpartum haemorrhage	Oral misoprostol versus placebo/no intervention	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for using ergometrine control as "no intervention"
5 (3285) [19]	Need for additional medical treatment	Oral misoprostol versus placebo/no intervention	4	0	0	0	0	High	
at least 2 (at least 1000) [19]	Need for additional surgical treatment	Oral misoprostol versus placebo/no intervention	4	0	0	–1	0	Moderate	Directness point deducted for low event rate
4 (3300) [19] [40]	Postpartum haemorrhage	Oral misoprostol versus ergot compounds	4	0	0	0	0	High	
4 (2598) [19] [40]	Need for additional medical treatment	Oral misoprostol versus ergot compounds	4	0	0	0	0	High	
3 (1277) [19] [40]	Need for additional surgical treatment	Oral misoprostol versus ergot compounds	4	0	0	0	0	High	
4 (20,199) [19]	Mortality	Oral misoprostol versus oxytocin	4	–1	0	–1	0	Low	Quality point deducted for no statistical assessment of between-group difference in most RCTs. Directness point deducted for low event rate
13 (at least 25,145) [19] [41]	Postpartum haemorrhage	Oral misoprostol versus oxytocin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
11 (at least 24,310) [19]	Need for additional medical treatment	Oral misoprostol versus oxytocin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
8 (22,526) [19]	Need for additional surgical treatment	Oral misoprostol versus oxytocin	4	0	0	0	0	High	
4 (3805) [19] [42]	Postpartum haemorrhage	Oral misoprostol versus oxytocin plus ergot compounds	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
4 (3805) [19] [42]	Need for additional medical treatment	Oral misoprostol versus oxytocin plus ergot compounds	4	0	0	0	0	High	
2 RCTs (2413) [19] [42]	Need for additional surgical treatment	Oral misoprostol versus oxytocin plus ergot compounds	4	0	–1	–1	0	Low	Consistency point deducted for conflicting results. Directness point deducted for low event rates
1 (542) [19]	Postpartum haemorrhage	Rectal misoprostol versus placebo/no intervention	4	0	0	0	0	High	
1 (546) [19]	Need for additional medical treatment	Rectal misoprostol versus placebo/no intervention	4	0	0	0	0	High	
1 RCT (550) [19]	Need for additional surgical treatment	Rectal misoprostol versus placebo/no intervention	4	–1	0	0	0	Moderate	Quality point deducted for no statistical assessment of between-group difference
5 (3433) [19] [43]	Postpartum haemorrhage	Rectal misoprostol versus oxytocin	4	0	0	0	0	High	

Important outcomes	Adverse effects, Maternal morbidity, Mortality, Need for additional medical treatment, Need for additional surgical treatment, Postpartum haemorrhage								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
4 (1780) [19] [43]	Need for additional medical treatment	Rectal misoprostol versus oxytocin	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results
1 (223) [19]	Need for additional surgical treatment	Rectal misoprostol versus oxytocin	4	0	0	–1	0	Moderate	Directness point deducted for low rate of events
2 (1262) [19]	Postpartum haemorrhage	Rectal misoprostol versus oxytocin plus ergot alkaloids	4	0	–1	0	0	Moderate	Consistency point deducted for conflicting results for different outcomes
1 (793) [19]	Need for additional medical treatment	Rectal misoprostol versus oxytocin plus ergot alkaloids	4	0	0	0	0	High	
1 (120) [19]	Postpartum haemorrhage	Rectal misoprostol versus carboprost injection	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (120) [19]	Need for additional medical treatment	Rectal misoprostol versus carboprost injection	4	–1	0	0	+2	High	Quality point deducted for sparse data. Effect-size points added for RR >5
1 (100) [44]	Postpartum haemorrhage	Vaginal misoprostol versus placebo/no intervention	4	–2	0	0	0	Low	Quality points deducted for sparse data and for no significant assessment of between-group differences

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.